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PROGNOSIS IN UVEAL MELANOMA*†

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THE material recorded in this study represents the total number of cases of uveal melanoma seen at the Royal London Ophthalmic Hospital and at the Royal Eye Hospital, London, during 1925 to 1939, except for a few specimens that could not be traced. In some cases the ultimate outcome was known, but in most the end result had to be ascertained from the records of the Registrar General. This study, therefore, largely hinges on the reliability of such records. It is generally assumed that they are of a high degree of accuracy—an assumption borne out by the fact that a test group of 20 cases, equally divided between those known to

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have died and those known to have survived, checked up accurately against the findings of the Registrar General. In all cases (a total of 285) the type of cell and in all but two cases the amount of pigment contained could be assessed. The investigation of reticulin was restricted to 150 cases. The classification used is largely that employed by Callender and his associates, in which spindle cell A. is Grade 1, spindle cell B. Grade 2, mixed cells Grade 3, and epithelioid cell is Grade 4. A few cases showed spindle cell B. in a fascicular arrangement, and in a few others the cells were necrotic and did not allow of a clear differentiation. Pigment content was assessed as light, medium, or heavy, and reticulin graded as: trace, light, medium, and heavy. Figures 1 to 10 are illustrative.

1. STATISTICAL ANALYSIS

A Series of 250 Cases of Melanoma of the Choroid

A detailed analysis is given in the Tables in the Appendix. The following are the salient points:—

1. *Age distribution* (248 cases).—There were no cases in the age group 0—9; there were only 3 cases in the age group 10—19. The subsequent decades gave an increasing number, but 53 per cent. of the total of cases were concentrated in the two decades 50—69. The mean age at excision of the eye was $53{\cdot}71 \pm 0{\cdot}90$. There was some slight difference in the age incidence as between men and women, but this was not statistically significant, as can be seen from Table I in the Appendix.

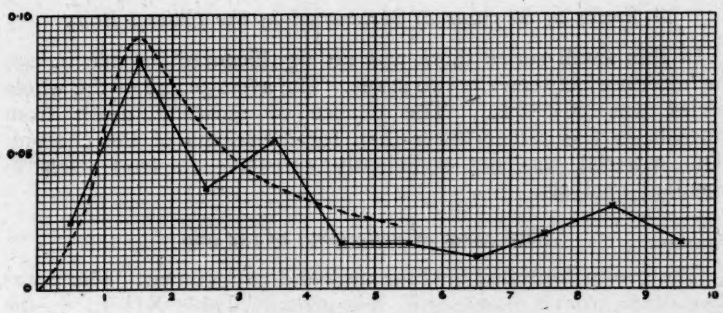
2. *Sex distribution* (250 cases).—No accurate assessment was possible as the relative male and female populations from which the cases were drawn was not known. Indirect computations (as seen in Table II of the Appendix) indicate that there is nothing to suggest that the incidence of melanoma is higher in one sex than in the other.

3. *Histological Components.*—As can be seen from Table III spindle cell B. was the commonest cell type with 59·6 per cent. of the total of cases. Tumours with mixed cells account for 17·6 per cent., and epithelioid cells for 8·8 per cent. Heavy pigment was uncommon accounting for 13·7 per cent., whilst light and medium pigment were fairly equally represented with 41·5 per cent. and 44·8 per cent. each. Heavy reticulin was likewise uncommon (8·3 per cent.); the other extreme—a trace of reticulin—was more common (19·5 per cent.) but light and medium distribution were the most frequent (39·1 per cent. and 33·1 per cent. respectively).

There was little evidence of any definite correlation between

the different histological components, apart from a tendency for tumours with epithelioid cells to be heavily pigmented.

4. *Mortality generally* (250 cases).—The chance of escaping death from metastases in the first five years was 0·822 for males and 0·795 for females, with 0·807 for both sexes combined. The odds declined somewhat if taken for a period of the first ten years, being 0·733, 0·734, 0·734 for males, females and both sexes together respectively (Table IV). The highest mortality occurred in the second year (see graph). Statistically there was no significant sex difference in mortality.



Duration (in years) from excision

Central death ratio (*m*). (Ratio of deaths from cancer to mean lives exposed during the year). The discontinuous line indicates the underlying trend. In view of the restricted data no attempt was made to fit a curve of a specific mathematical law but an approximation thereto was obtained by drawing a curve through the observed values by graphic graduation.

5. *Effect of age on prognosis* (248 cases).—When three broad age groups were taken—under 40, 40—59, and 60 and over—a statistically significant increase in mortality from mestastases with advancing age was observed for the first five years. The odds against the fatal recurrence of cancer shortened from 9 : 1 to 7 : 1 between the youngest and oldest age groups (Table V).

6. *Mortality according to type of cell* (250 cases).—No statistical significance could be attributed to the variation in mortality with the different types of cell except for epithelioid cells, the mortality from which was distinctly higher (Table VI).

7. *Mortality according to pigment* (248 cases).—A statistically significant lower mortality was found to be associated with a low pigment content (Table VII).

8. *Mortality according to reticulin* (133 cases).—There was a significant correlation between high mortality and low reticulin content (Table VIII).

9. *Mortality by cell and pigment* (248 cases).—Within each pigment group there was little variation with different types of cell apart from epithelioid cells. Within each cell grade low mortality was associated with light pigment content (Table IX).

10. *Cell, pigment and reticulin combinations* (133 cases).—It appears likely that each of the factors has an independent effect on prognosis, but that cell grade is less important than pigment or reticulin. The determination of the partial association of mortality with each of the three factors cannot be reliably made on the data of the present series (Table X).

A Series of 30 cases of Melanoma of the Ciliary Body

In this small series there was no significant difference in age or incidence between the two sexes. The average age of the whole series was 56·3±3·1. The chance of escaping death from metastases was rather lower than for melanoma of the choroid. The material was not sufficiently extensive to lend itself to detailed analysis.

Five cases of melanoma of the iris

The group consisted of three men and two women. There was one death from metastases in this group. Table XII shows the salient features observed in this small series.

2. COMPARATIVE STUDIES ON CHOROIDAL MELANOMA

The considerable literature on prognosis in uveal melanoma is unfortunately largely vitiated owing to the general lack of statistical assessment of the results obtained. Comparative studies of results obtained by different observers also present difficulties owing to the lack of uniformity in criteria used; the older literature is largely inapplicable, particularly since recent studies have shown the significance of reticulin in the assessment of prognosis. Only partial comparison with the variously recorded results is, therefore, possible.

1.—*Age distribution.* The following summary table shows the age distribution in our own series compared with those published by Callender, Wilder and Ash (1942) and Pahwa (1941). The first represents an extensive study covering 1,418 cases observed in the United States. The second deals with 100 cases seen at the Royal London Ophthalmic Hospital between 1930 and 1935—a group covered by our own series.

These three series give essentially the same data: melanoma of the choroid is concentrated in the age groups 40—70.

	Callender, Wilder & Ash. 1,418 cases. per cent.	Pahwa 100 cases. per cent.	Present series. 250 cases. per cent.
0-9	0·14	—	—
10-19	0·92	—	1·21
20-29	5·01	6·3	4·44
30-39	13·33	11·6	12·50
40-49	20·87	22·1	18·55
50-59	26·44	25·3	25·40
60 69	23·13	23·1	27·82
70-79	9·17	11·6	9·27
80-89	0·92	—	0·81
90 and over	0·07	—	—
	100·00	100·0	100·00
Mean age	52·76	53·7	53·71

2.—*Sex distribution.* In 1,550 cases noted by Callender, Wilder and Ash there were 799 men and 751 women. It would appear that their series is not consecutive, but a random selection. In their findings, as in ours, there is nothing to suggest that there is a significant sex difference.

3.—*Cell type.* The following summary table shows the distribution of cell type in the comparable series:—

	Callender, Wilder & Ash.	Pahwa	Terry & Johns	McKee	Present Series.
Spindle A.	35	22	6	14	11
Spindle B.	117	7	12	—	149
Mixed	276	29	31	2	44
Epithelioid	14	25	8	7	22
Fascicular	13	9	8	4	18
Necrotic	45	—	—	—	6
	500	92	65	27	250

The series given by Callender, Wilder and Ash and also that of Pahwa and of Terry and Johns contained a high proportion of mixed tumours reducing the proportionate incidence of other cell

types. Our series shows a high incidence of spindle B. types. The proportion of epithelioid cell tumours in our series is distinctly higher than in the American series, though lower than in the other small series.

4.—*Pigment.* The following summary table shows the comparative incidence of pigment in a series recorded by Callender, Wilder and Ash, and by ourselves:—

	Callender, Wilder & Ash.	Present Series.
Pigment		
Light	141	103
Medium	235	111
Marked	111	34
Heavy	13	
	500	248

It will be noted that there is a greater incidence of marked and heavy pigment in the first series.

5.—*Reticulin content.* The significant studies on reticulin are those that have come from Callender and his associates. The small series of 41 cases published by McGregor and Hill does not lend itself to statistical assessment; their general conclusion that a low reticulin content is disadvantageous is also brought out in the 61 cases recorded by Pahwa. The distribution of reticulin in the series by Callender, Wilder and Ash, and our own, are shown in the following summary table:—

Reticulin content	Callender, Wilder & Ash	Present Series.
Heavy	19	11
Marked	90	
Medium	143	44
Light	223	52
Absent	25	26*
	500	133

*Absent or trace.

Our series would appear to contain more cases with low reticulin content.

6.—*Prognosis in general.* As different series of cases appear to contain different proportions of the constituent histological elements it would seem that the assessment of prognosis is difficult unless one is sure that the various series are comparable and unselected. Moreover, the time at which the affected eye was removed may vary in different statistical computations. Our own series gives a distinctly good prognosis, the survival rate for a period of five years being 80·7 per cent., and 73·4 per cent. for ten years. Callender, Wilder and Ash (1942) give a survival rate of 52 per cent. for five years and 34 per cent. for ten years, but their findings are open to the statistical criticism that they have not dealt with the cancer mortality within a definite period. Martin-Jones, likewise, obtained a poorer prognosis than our series shows. His survival rate for a period of five years is 64·2 per cent., and for a period of ten years 44·5 per cent. Recalculating his data on the basis of chance of escaping death from cancer during X years following excision, his percentages are raised nearer to ours, being 67·2 and 53·0 respectively. Pahwa's total mortality from secondary growth (for material overlapping ours, but in which mortality was assessed by direct enquiry) approaches ours still more closely. Closer still is the mortality of about 26·5 recorded by Hippel (1930) in a collected series of 609 cases.

7.—*Prognosis in relation to histological components.* Callender, Wilder and Ash found that prognosis varies directly with cell type, pigment content and reticulin content. For a five-year period there was a mortality of 6 per cent. with spindle cell A., 25 per cent. with spindle cell B., 62 per cent. with mixed tumours and 71 per cent. with tumours composed of epithelioid cells; tumours with spindle cell B. in fascicular arrangement and those with necrotic cells gave a mortality of 38 per cent. and 49 per cent. respectively. The mortality from tumours containing light, medium, marked and heavy pigment was respectively 34, 51, 55 and 69 per cent. Mortality decreased with increase of reticulin content. It was 80 per cent. when reticulin was absent, and 55, 44, 36 and 10 per cent. when the reticulin content was light, medium, marked and heavy respectively. It is unfortunate that their assessment is not made by a statistical analysis which takes account of period of observation. Our own findings are distinctly more limited: a statistically significant increased mortality in relation to epithelioid cells, a lower mortality with light pigment content, a higher mortality with low reticulin content.

8.—*Age in relation to prognosis.* Callender, Wilder and Ash suggest that the worse prognosis is in the higher age group. Martin-Jones also finds a less favourable prognosis at older ages. Our statistical evaluation shows the same trend.

3. DISCUSSION

Judging by the older literature, prognosis in uveal melanoma has improved steadily during the last seventy years. Thus, Hirschberg gives the survival rate as 25 per cent. in 1882, 35 per cent. in 1895, and 56 per cent. in 1903. References to further data of this type are given by v. Hippel (1930) and Teraskeli (1928). Continental studies have been largely concerned with the stage of growth and its bearing on prognosis, stage I representing the phase when the tumour is confined to the uveal tract, stage II when it has penetrated into the ocular tunics, and stage III when it has perforated these. (In another classification stage I is the quiet eye, stage II the secondary glaucomatous process, stage III orbital invasion, stage IV dissemination.) Studies on these lines have led to rather sterile discussions as to the best time for removing the affected eye. The great merit of Callender's work at the American Registry of Ophthalmic Pathology is that in the first place he introduced an adequate classification (and possible grading) of cell type (Callender, 1931), and that secondly he established the significance of reticulin as a prognostic factor in uveal melanoma (Callender and Wilder, 1935). These excellent pathological studies, recorded in three successive papers, covered at first 111 cases (Callender, 1931), subsequently 253 cases (Wilder and Callender, 1939), and more recently 500 cases (Callender, Wilder and Ash, 1942). It is unfortunate that in rightly stressing the need for adequate histological detail, Callender and his associates have tended to overlook the grosser—but necessary—criteria implied in the classification by stages.

Our data do not suggest that there is any correlation between the three histological components, except that tumours with epithelioid cells tend to be heavily pigmented. Since heavy pigmentation is regarded as an unfavourable prognostic feature, the unfavourable effect of epithelioid cells is emphasized.

If choroidal melanomata are therefore to be regarded as consisting of three freely variable components, it is clear that prognosis must be assessed on the basis of each of the components. In addition, the behaviour of the tumour as a whole must also be taken into account. As long as a true measure of prognosis is not available it is impossible to indicate whether exenteration

Figs 1-4 to illustrate cell types

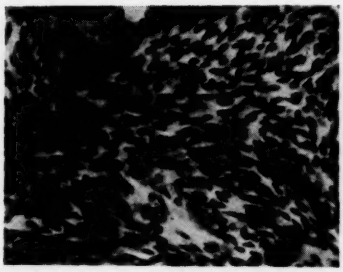


FIG. 1 Spindle cell A
(Magnification ×160)

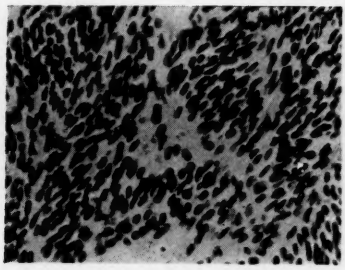


FIG. 2. Spindle cell B
(Magnification ×160)

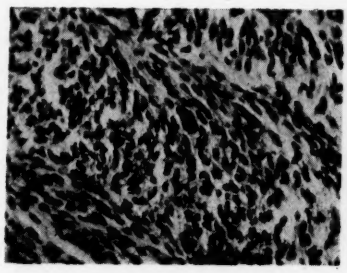


FIG. 2*a*. Spindle cell B, fascicular arrangement (Magnification ×160)

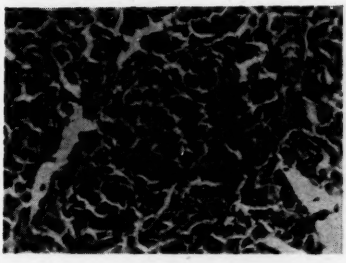


FIG. 3. Mixed cells
(Magnification ×160)

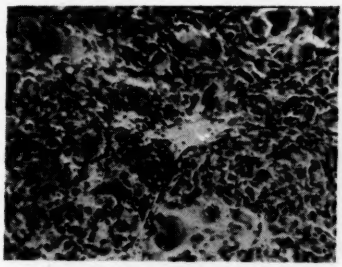


FIG. 4. Epithelioid cells
(Magnification ×80)

Figs. 5-7 to illustrate pigment content. Figs. 8-10 to illustrate reticulin content

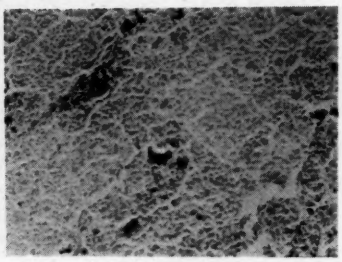


FIG. 5. Light pigment content (Magnification ×80)

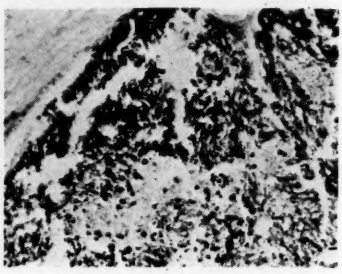


FIG. 6 Medium pigment content (Magnification ×40)

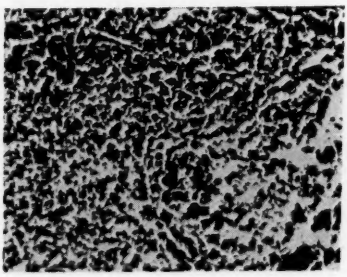


FIG. 7. Heavy pigment content (Magnification ×40)

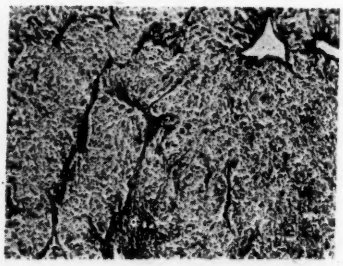


FIG. 8 Light reticulin content (Magnification ×40)

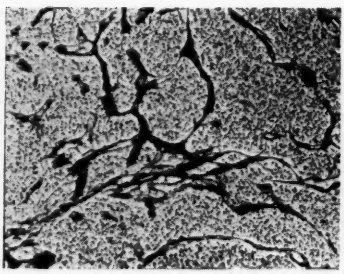


FIG. 9. Medium reticulin content (Magnification ×40)

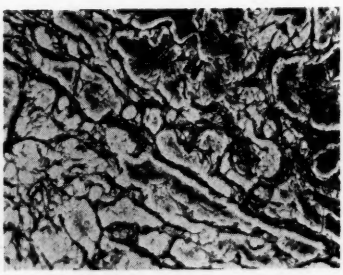


FIG. 10. Heavy reticulin content (Magnification ×40)

of the orbit rather than excision of the globe, or possibly radiotherapy, is the proper treatment. It would seem essential that in the further collection of pathological material uniform criteria should be employed. These criteria might well be:—

(i) Histological. The classification employed by Callender and his associates is eminently satisfactory for cell type. The grouping of pigment into four quantitative groups is probably an unnecessary refinement; in practice a classification into light, medium and heavy is easier and probably more reliable. Likewise with reticulin: the distinction between marked and heavy seems unnecessary and rather troublesome.

(ii) Gross features in the tumour. Vascularity, haemorrhage and necrosis all need to be noted.

(iii) Extension beyond the uvea. Extension into the ocular tunics, the emissary vessels and into the orbit also need to be recorded.

The classification into stages is now largely a matter of historical interest. Eyes with melanoma of the choroid are generally removed in what constituted stage I, so that as many distinctive components as possible in addition to histological features have to be isolated and studied. It should be redundant—but nevertheless it appears to be necessary—to add that proper statistical evaluation of the collected material is also essential.

Summary

(1) A series of 250 cases of melanoma of the choroid, 30 cases of melanoma of the ciliary body, and 5 cases of melanoma of the iris was studied histologically and correlated with mortality from metastases.

(2) Fifty-three per cent. of all cases of choroidal melanoma were concentrated in the two decades 50—69 years. The mean age at excision of the eye for the whole series was 53·71±0·90. There was no statistically significant sex difference in age distribution or incidence. Histologically spindle cell B. predominated, accounting for 59·6 per cent. of the total of cases. Spindle cell A. accounted for 4·4 per cent., mixed cells for 17·6 per cent., epithelioid cells for 8·8 per cent., spindle cell B. in fascicular arrangement for 7·2 per cent., and necrotic tumours for 2·4 per cent. Heavy pigment was present in 13·7 per cent., whilst light and medium pigment distribution gave 41·5 and 44·8 per cent. respectively. Reticulin, studied in 133 cases, was present in heavy amounts

in only 8·3 per cent. A trace of reticulin was present in 19·5 per cent., whilst light and medium reticulin distribution was observed in 39·1 per cent. and 33·1 per cent. respectively. Apart from a statistically significant association of heavy pigment with epithelioid cells, there was no evidence of any other correlation between the histological components. The chance of escaping death from metastases in the first five years was 0·807 for the series as a whole, declining to 0·734 for a period of ten years. The highest mortality occurred in the second year after excision. There was a statistically significant better prognosis in the younger age groups. No statistical significance could be attributed to variation in mortality with different types of cells, except that epithelioid cells carried a worse prognosis. A low mortality was found associated with a low pigment content, and a high mortality with low reticulin content. Each of the three histological components appears to have an independent, but not equally forcible, effect on prognosis, so that mortality is influenced to some extent by cell grade, but more by pigment and reticulin content. The main prognostic factors as they emerge from this study are: a favourable effect from light pigment content, and an unfavourable effect from epithelioid cells and from low reticulin content. These general conclusions support the findings of Callender and his associates, though they are not as emphatic as theirs.

(3) A study of the 30 cases of melanoma of the ciliary body suggests that mortality from this type of tumour is rather higher than for melanoma of the choroid.

(4) The importance of studying the stage of development of the tumour in addition to its histological features is stressed.

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APPENDIX—STATISTICAL ANALYSIS

1.—Melanoma of the choroid

1. *Age distribution.*—Table I shows the sex and age distribution of the series at excision, together with the mean ages and standard deviations.

TABLE I—*Sex and age distribution of cases of melanoma of the choroid.*

Age	Males	Females	Total	
			No.	Per cent.*
0 —	—	—	—	—
10 —	2	1	3	1·21
20 —	4	7	11	4·44
30 —	11	20	31	12·50
40 —	18	28	46	18·55
50 —	32	31	63	25·40
60 —	34	35	69	27·82
70 —	13	10	23	9·27
80 —	1	1	2	0·81
Not stated	1	1	2	—
Total	116	134	250	100·00
Mean age	55·26 ± 1·31	52·37 ± 1·22	53·71 ± 0·90	

* Based on 248 stated cases only.

In the actual samples the mean age at excision is less for females than for males, but this difference is not statistically significant and there is no evidence of association between sex and age.

The analysis of the variance of age is as follows:—

	Degrees of freedom	Sum of squares	Mean square
Between sexes	1	515·98	515·98
Residual	246	48,671·12	197·85
	247	49,187·10	

The probability that the difference in variance estimates is attributable to sampling fluctuation exceeds 0·10.

The mean age at excision may therefore be estimated at 53·71 ± 0·90 years.

2. *Sex distribution.*—The relative male and female populations from which the cases were drawn is not known and therefore the sampling error of the numbers for each sex cannot be accurately assessed, but it will be seen from Table II that the ratio of male to female cases in any age group is not inconsistent with that operating in the general population of England and Wales.

TABLE II—*Sex incidence.*

Age	Male cases	Ratio of females to males in England and Wales census 1931	Expected female cases on basis of census ratios	Actual female cases	Actual — expected	Approx. standard error of expected female cases*
10 —	2	0·995	1·99	1	— 0·99	1·40
20 —	4	1·059	4·23	7	+ 2·77	2·11
30 —	11	1·157	12·72	20	+ 7·28	3·84
40 —	18	1·160	20·87	28	+ 7·13	4·92
50 —	32	1·115	35·69	31	— 4·69	6·31
60 —	34	1·159	39·41	35	— 4·41	6·76
70 —	13	1·360	17·69	10	— 7·69	4·91
80 —	1	1·782	1·78	1	— 0·78	1·78
Not stated	1	—	1·09	1	— 0·09	1·09
Total	116	1·088	127·31	134	+ 6·69	11·72

* On assumption stated in text.

In the above table the variance in the expected female cases due to the application of the census ratios to the unknown portion of the population included in the sample is ignored, and account is taken only of the sampling error of the number of male cases in each group. The standard error in the estimate of the female cases arising from this is shown in the final column and is taken as approximately $r \times \sqrt{M}$ where r=census sex ratio, M=actual male cases. It will be seen that the excess or deficiency in the actual female cases in any age group is in no instance greater than twice this standard error. The systematic character of the differences in the penultimate column of the table (at first positive then negative) reflects the fact that the females are as a group younger than the males in this series, though this difference has been shown not to be statistically significant. It would appear that the incidence of melanoma cannot be regarded as any greater in one sex than the other.

TABLE III—*Histological Components.*

	Males	Females	Persons	Percentage
Cell type (250 cases)				
Spindle Cell A.	5	6	11	4·4
Spindle Cell B.	71	78	149	59·6
Mixed	17	27	44	17·6
Epithelioid Cell	10	12	22	8·8
Spindle Cell B. fascicular	12	6	18	7·2
Necrotic	1	5	6	2·4
				100·0
Pigment (248 cases)				
Light	49	54	103	41·5*
Medium	52	59	111	44·8*
Heavy	14	20	34	13·7*
				100·0
Reticulin (133 cases)				
Trace	11	15	26	19·5*
Light	26	26	52	39·1*
Medium	23	21	44	33·1*
Heavy	5	6	11	8·3*
				100·0

* Of stated cases.

3. *Histological components.*—The type of cell could be established in all cases, the degree of pigmentation in all but two cases, and reticulin content in 133 cases. The sub-joined table shows the findings obtained.

The possibility of association between the three components was investigated by independence tests of the chi square type. There appeared to be a significant association of heavy pigment content with epithelioid cells, but no other significant finding emerged.

TABLE IV—*Survivorship factors.*

Year of survival	Males			Females			Both sexes combined		
	Mean exposed	Deaths from metastases	Chance of escaping death from cancer	Mean exposed	Deaths from metastases	Chance of escaping death from cancer	Mean exposed	Deaths from metastasis	Chance of escaping death from cancer
x	E	θ	P_x	E	θ	P_x	E	θ	P_x
0 —	113	4	0·965	132	2	0·985	245	6	0·976
1 —	106·5	6	0·945	123·5	13	0·900	230	19	0·921
2 —	99	6	0·941	115·5	2	0·983	214·5	8	0·963
3 —	93·5	2	0·979	109·5	9	0·921	203	11	0·947
4 —	89	2	0·978	104·5	1	0·991	193·5	3	0·985
Chance of escaping death from cancer in the first five years :—			0·822			0·795			0·807
5 —	84·5	1	0·988	102·5	2	0·981	187	3	0·984
6 —	78	—	1·000	95·5	2	0·979	173·5	2	0·989
7 —	68·5	2	0·971	84·5	1	0·988	153	3	0·981
8 —	59·5	2	0·967	75	2	0·974	134·5	4	0·971
9 —	49·5	2	0·960	66·5	—	1·000	116	2	0·983
Chance of escaping death from cancer in the first ten years :—			0·733			0·734			0·734

The survivorship factor $P_x = \frac{2 - M}{2 + M}$ — where $M = \frac{\theta}{E}$, and the chance of escaping death from cancer during the first five or ten years is given by the product of the first five or ten of the series of values of P_x.

4. *Mortality generally.*—The cases have been analysed according to the number of years observed since excision. The deaths from metastases occurring between x and x±1 years after excision have been related to the mean number of patients exposed to risk of death from cancer during that year leading to the calculation of the chance of escaping death from cancer in each of the consecutive years following excision. The principal details (up to 10 years) are shown in Table IV.

The difference between the five year factors for males and females is not significant, as will be seen from the following test.

	Mean exposed / E	Deaths from metastases / θ	Central death rate / $M = \theta/E$	Expected deaths / $\theta^1 = E \times M$	$\theta - \theta^1$	$\frac{(\theta - \theta^1)^2}{E \times M(1-M)} = \chi^2$
			(both sexes)			
Males	100·2	20	—	21·68	— 1·68	0·166
Females	117·0	27	—	25·32	+ 1·68	0·142
Total	217·2	47	0·2164	—	—	0·308
						P = 0·58

In calculating the exposed to risk for any particular year, deaths whether from metastases or from other causes were given six months' exposure.

The graph, in the text illustrates the variation of the risk of death from metastases according to duration after excision. The continuous curve connects the observed values of the ratio of deaths from metastases in each year to lives exposed during the year (M) (both sexes combined). The irregularity is, of course, inevitable in view of the small numbers involved. The general trend is indicated by the discontinuous line. In view of the restricted data no attempt was made to fit a specific mathematical law, but an approximation thereto was obtained by drawing a curve through the observed values by inspection. The risk of metastases rises to a peak in the second year and thereafter falls fairly rapidly.

5. *Effect of age on prognosis.*—The chance of escaping death from metastases during the first five years following excision was calculated separately for each of three broad age groups—under 40, 40-59, 60 and over. A statistically significant increase in mortality with advancing age takes place as indicated in the following table.

TABLE V—*Mortality in age groups—first five years.*

Age group	Mean lives exposed	Deaths from metastases	Expected deaths on the assumption of no association with age.	Actual — expected	Chance of escaping death from cancer.
Under 40 ...	42·5	4	9·16	— 5·16	0·910
40 — 59 ...	100·5	15	21·67	— 6·67	0·861
60 and over ...	75·0	28	16·17	+ 11·83	0·685

Using Yates' correction — χ^2 = 15·38 $P < 0{\cdot}0005$.

There were no significant differences between the two sexes in any age group. It will be seen that the odds against the recurrence of cancer in the first five years shorten from 9:1 to 7:1 between the youngest and the oldest age group.

6. *Mortality according to type of cell.*—In Table VI the mortality data for the first five years are analysed according to the cell type of the melanoma, and actual deaths from metastases in each group are compared with those expected on the assumption that mortality is not associated with cell.

TABLE VI—*Cancer mortality by cell grade — first five years. (both sexes combined).*

Grade of cell	Mean lives exposed	Deaths from metastases	Expected deaths (assuming no association with cell grade)	Actual — Expected
1 (Spindle A)	10·5	1	2·24	— 1·24
2 (Spindle B)	131·5	25	28·09	— 3·09
3 (Mixed)	39·0	8	8·33	— 0·33
4 (Epithelioid)	17·5	8	3·74	+ 4·26
2 Fascicular	16·5	3	3·53	— 0·53
Necrotic...	5·0	2	1·07	+ 0·93
Total...	220·0*	47	47·00	—

*This differs from the average in Table IV because for the purpose of the above table the data are not analysed according to the individual years of the period.

Of the differences in the final column of this table that for Grade 4 alone can be regarded as statistically significant. Comparing the cancer mortality in this grade with that of the remainder, we find $P_s^2 = 0{\cdot}0096$.

7. *Mortality according to pigment.*—When the melanomata are classified by pigment the mortality experience in the first five years is as shown in Table VII.

TABLE VII—*Mortality by pigment—first five years (both sexes combined).*

Pigment	Mean lives Exposed	Actual deaths from metastases	Expected deaths (assuming no association with pigment	Actual — Expected
Light	94·5	9	19·16	— 10·16
Medium	92·5	28	18·76	+ 9·24
Heavy	30·0	7	6·08	+ 0·92
Total	217·0	44	44·00	—

$\chi^2 = 12{\cdot}64$ P = 0·002

It appears that lower mortality is associated with light pigment.

8. *Mortality according to reticulin content.*—The reticulin content was not stated in all cases and the mortality data are scanty, but the following analysis suggests that higher mortality is associated with low reticulin content. The

TABLE VIII—*Mortality by reticulin content first five years (both sexes).*

Reticulin	Mean lives exposed	Actual deaths from metastases	Expected deaths (assuming no association with reticulin content)	Actual — Expected
Trace or light	61·5	26	15·65	+ 10·35
Medium	41·0	2	10·43	— 8·43
Heavy	11·5	1	2·92	— 1·92
Total stated	114·0	29	29·00	—

differences between actual and expected deaths for the first two groups are greater than twice the standard errors involved, and the differences are significant.

9. *Mortality by cell and pigment.*—In Table IX the mortality experience in the first five years is subdivided according to cell grade and pigment and the ratios of deaths to lives exposed are given. The numbers involved are small and in only a few cases which have been underlined do the ratios differ significantly from that based on total deaths and total exposures.

In the "light pigment" group, the ratios for the different cell grades are very close to that for the "light pigment" group as a whole with the exception of grade 1 and the necrotic type where there were no deaths and grade 4 where the ratio was higher though not significantly. For medium pigment there is uniformity except for grades 4 and 2—fascicular where the ratios are higher than that for the medium pigment group as a whole (significant for grade 4). For heavy pigment, grade 4 alone shows a ratio higher (though not significantly so) than the group ratio. Within each pigment group therefore there is very

TABLE IX—*Mortality from metastases by cell and pigment first five years (both sexes combined).*

Cell grade	Pigment											
	Light			Medium			Heavy			Total		
	E	θ	M	E	θ	M	E	θ	M	E	θ	M
1	6	—	—	3·5	1	0·29	1	—	—	10·5	1	0·10
2	62·5	6	0·10	53·0	14	0·26	14	2	0·14	129·5	22	0·17
3	11·5	1	0·09	20·5	6	0·29	6	1	0·17	38	8	0·21
4	3	1	0·33	8	4	0·50	6·5	3	0·46	17·5	8	0·46
2 Fascicular ...	10·5	1	0·10	4	2	0·50	2	—	—	16·5	3	0·18
Necrotic ...	1	—	—	3·5	1	0·29	0·5	1	2·0	5	2	0·40
Total	94·5	9	0·10	92·5	28	0·30	30	7	0·23	217	44	0·20

(1) E = mean exposed. θ = deaths metastases. M = θ/E.

(2) Discrepancies with Table 6 are due to the exclusion of cases in which the pigment is not stated.

little variation of mortality with cell grade apart from grade 4. On the other hand when the effect of pigment within each cell grade is inspected it will be seen that low mortality is associated with light pigment in every instance.

This analysis suggests that while the observation of light pigment is by itself an indication of light mortality, no inference as to mortality may be drawn from cell grade alone (except perhaps for grade 4); it is necessary also to determine the pigment.

10. *Cell, pigment and reticulin combinations.*—The numbers were too small to bring reticulin into account in the above mortality analysis, but Table X shows the analysis of the whole series by cell, pigment and reticulin content excluding those in which all three factors were not recorded.

TABLE X—*Analysis of series according to cell, pigment, reticulin.*

Reticulin	Cell 1 Pigment L M H	Cell 2 Pigment L M H	Cell 3 Pigment L M H	Cell 4 Pigment L M H	Cell 2 Fascicular Pigment L M H	Necrotic Pigment L M H	Total Pigment L M H
Trace or light	2 1 1	24 11 7	3 4 3	2 4 3	8 2 2	— — 1	39 22 17
Medium	1 1 —	12 19 —	3 2 2	— 1 1	1 1 —	— — —	17 24 3
Heavy	2 — —	4 3 1	— — —	— — —	1 — —	— — —	7 3 1
Total	8	81	17	11	15	1	133
Per cent. "Trace or light"	50	52	59	82	80	(100)	59

If these figures are representative of the whole series, the following inferences may be drawn:—

(i) It might be suggested that the high mortality in epithelioid cell-type cases was due to light reticulin content. A rough test can be made from Table X,

assuming that these figures (which are only a fraction of the total exposed-to-risk in the series) are yet representative of the whole series.

Considering the distribution of Table X, viz.:—

Reticulin	Cells					
	1	2	3	4	F+N	Total
L	4	42	10	9	13	78
M	2	31	7	2	2	44
H	2	8	—	—	1	11
	8	81	17	11	16	133

If these numbers were exposed to the mortality of Table VIII, *i.e.*, if the reticulin content were the only factor and mortality was unaffected by cell-type, we should get the following expected deaths and death-rates:—

Expected deaths on reticulin mortality.

Reticulin	Cells				
	1	2	3	4	F + N
L	1·7	17·8	4·2	3·8	5·5
M	0·1	1·5	0·3	0·1	0·1
H	0·2	0·7	—	—	0·1
	2·0	20·0	4·5	3·9	5·7
Hypothetical mortality rates	0·25	0·25	0·26	0·35	0·36
Actual rates (Table 6)	0·10	0·19	0·21	0·46	0·23

There is a substantial difference between "hypothetical" and actual rates in cell grade 1 and in the fascicular-necrotic group, though it has to be borne in mind that the actual rates are here based on small numbers. On the whole the impression is gained that the cell grade may be an independent factor in prognosis but is not such an important one as reticulin or pigment. This is not a conclusive finding, however, and requires confirmation.

(ii) In the pigment groups the percentages with "trace or light reticulin" are as follows:—

Light pigment	...	...	62
Medium „	...	...	45
Heavy „	...	...	79

The mortality experience of the light pigment group is not, therefore, explicable on the hypothesis that the reticulin with which it is associated is the causative factor, as this would lead to the expectation of heavier mortality in the light pigment group than in the medium pigment group instead of the lighter mortality actually observed.

(iii) Conversely the heavy mortality associated with light reticulin does not arise from association between reticulin and pigment or cell. If the rates of Table IX are weighted with the proportions of Table X, the death-rates for the reticulin groups, if cell grade and pigment were the only operating factors, would be as shown below. The *actual* rates are quite different.

	Central death-rate (θ/E)	
	"Expected"	Actual
Trace or light reticulin...	0·20	0·42
Medium	0·21	0·06
Heavy	0·13	

(iv) It appears likely that each of the factors has an independent effect on prognosis but that cell grade is less important than pigment or reticulin content. The determination of the partial association of mortality with each of the three factors cannot be reliably made on the data of the present series.

2.—Melanoma of the ciliary body

1. *Age and sex distribution.*—There were only 30 cases in this series, the age and sex analysis being as follows:—

Age	Males	Females
20—	1	2
30—	2	1
40—	2	2
50—	3	2
60—	3	5
70—	3	3
80—	1	—
Total	15	15

There is no significant difference in age or incidence between the two sexes. The average age of the whole series is 56·3±3·1.

2. *Mortality.*—The chances of escaping death from metastases in the first five and ten years following excision, calculated in the same way as for melanoma of the choroid (except that individual years of the periods were not observed separately), are as set out below:—

Chance of escaping death from metastases in X years.

X	Males	Females	Both sexes
5	0·459	0·739	0·601
10	0·345	0·484	0·412

Differences in these factors between males and females arise in the first five years. The details are:—

Years	Males			Females			Difference between sexes
	Mean exposed / E	Deaths from cancer / θ	M = θ/E	Mean exposed / E	Deaths from cancer / θ	M = θ/E	
0 — 4	10·8	8	0·741	13 3	4	0·301	Significant
5 — 9	3·5	1	0·286	7·2	3	0·417	Not significant

It appears that metastases occurred later in females than in males.

In such a small series, the sampling errors arising in an analysis of mortality by cell grade or pigment or reticulin content were relatively large, and no statistically significant variations were found.

3. *Histological components.*—The following summary table gives the salient features observed:—

TABLE XI—*Ciliary Body: distribution of histological components.*

	Cell grade					Pigment			Reticulin				
	1	2	3	4	2 Fasc.	Light	Medium	Heavy	Trace	Light	Medium	Heavy	Not stated
M.	1	7	4	3	—	4	9	2	2	3	2	—	—
F.	1	7	2	2	3	6	3	6	4	3	2	—	—
P.	2	14	6	5	3	10	12	8	6	6	4	—	14

The distribution of these components is not substantially different from that observed in choroidal melanoma.

3.—Melanoma of the iris

The following summary table gives the available information on the five cases in this series:—

TABLE XII—*Findings in five cases of melanoma of the iris.*

	Age	Cell	Pigment	Reticulin	Outcome
Males	18	Spindle B.	Medium	Not stated	Alive 6 years later.
	51	,, ,,	,,	,,	Alive 20 years later.
	71	,, ,,	Heavy	Heavy	Alive 14 years later.
Females	52	Spindle B.	Light	Not stated	Died from metastases within 2 years.
	60	,, ,,	Medium	,, ,,	Died 12 years later from cerebral thrombosis.

The one case with death from metastases was vascular histologically.

DOUBLE STAINING FOR BULK SPECIMENS OF RETINA AND CHOROID*

BY

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PUBLICATIONS from the Tennent Institute (A. J. Ballantyne, 1941) have shown that in the anatomical investigation of pathological fundus changes, unless we follow a certain routine we run the risk of missing essentials. Slit-lamp examination of the optic nerve and retina is the first step. Ample use of the clearing method of retinal tissue is the second in the scheme described by Loewenstein, 1942.

This method made possible the discovery of microaneurysms in the retina of diabetics with no signs of retinopathy (A. J. Ballantyne and A. Loewenstein, 1944, *a* and *b*).

Study of the cleared unstained retina in bulk was a great help in the investigation of hypertensive retinopathy, of new formed intra-, pre- and retro-retinal vessels, of thrombotic changes, of vasculitis retinæ, and many other diseases of the eye. It also led the way to the discovery of " cushion cells " in the capillaries, and of intramural vessels in the retinal vascular system (Loewenstein, 1946 and 1948).

The cleared unstained retina and choroid in bulk revealed a multitude of details.

But one of the greatest advantages of this method, which could be called the " simplest type of microscopical investigation," is undoubtedly the surview it provides of different pathological appearances, without inhibiting the study of the finest details. Thus, the close linkage of several changes became manifest in this simple manner, a linkage which could only have been proved otherwise by painstaking reconstruction of serial sections.

The range of detail we are able to perceive in unstained cleared specimens is increased if we make ample use of reduced illumination by closing down the iris diaphragm, and by dark adaptation of the observer. On the other hand, some parts of the specimen may demand more light. Microscopy of unstained bulk specimens cannot be approached in the " static " manner reserved for stained sections. It has to be performed " dynamically," one hand always being on the iris diaphragm.

And, last but not least, patience and far more time are required for a single specimen, as we are dealing with a tissue of considerable

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thickness. We therefore focus different layers. If we assume the thickness of a normal histological section to be 10μ we are investigating a tissue of approximately ten times the usual thickness, and each layer of about 10—20μ thickness has to be studied separately. Our work is three dimensional in contrast to the usual two dimensional routine microscopy. The use of a binocular eyepiece is recommended. Use of the phase microscope promising.

In spite of the improvements achieved, I soon felt that staining might increase contrasts, and add something to the elucidation of retinal anatomy. I have used a great many stains since I started this work eight years ago, without the desired result. Recently, more satisfactory results were obtained since I returned to haematoxylin and used a prolonged overstaining with a dilute solution, and washed in tapwater for ten minutes after careful removal of the vitreous with cotton wool. The specimen is placed into a stain consisting of 2—4 drops of the stock solution of haematoxylin in 5 ml. tapwater, and left in this solution 4—6 hours or longer at room temperature. Control under the microscope until overstaining is achieved. The specimen must appear dark bluish in water, and not translucent enough to distinguish details.

This staining sufficed to show beautifully the dark concentric lines in a case of pressure folds caused by a retrobulbar metastatic tumour. It shows ganglion cell distribution of the macular area and the nerve fibre pattern perfectly.

After rinsing in water, fat staining of the specimen is performed with Sudan IV. I now use the Kay and Whitehead technique with a stock solution in which 2 g. Sudan IV powder is dissolved in one litre of absolute ethyl alcohol at room temperature. It is boiled gently till all the powder is dissolved.

To 7 ml. of this stock solution, 9 ml. 50 per cent. alcohol is added. It is left at room temperature for an hour and filtered. The specimen is put into the filtrate and kept forty-five minutes in the incubator at 37° C. The specimen is washed in distilled water and examined in 50 per cent. glycerine.

I have abandoned the earlier used Spielmeyer technique, in which the specimen is heated till vapours rise. This higher temperature might do harm to the fine retinal structure, and specially to the distribution of fat.

If it is to be kept permanently, it can be framed with tempera or mounted in glycerine jelly to which several crystals of carbolic acid are added to keep off mould infection. This may still occur, unfortunately, after some years, in spite of carbolic acid addition.

The nuclei appear dark purplish, the whole vascular system standing out clearly in the purple mass of ganglion cells, and

nuclei of the inner nuclear layer. If we want to study the deepest retinal layers we turn the specimen upside down. We may achieve the same effect with a dry specimen turning the whole slide. The use of the highest powers of the microscope will depend then on the thickness of the used glass slide, and the focal distance of the front lens in the microscopic objective.

The capillaries are seen in their course, both the superficial network and the deeper one. It is interesting to observe the linkage between the two systems.

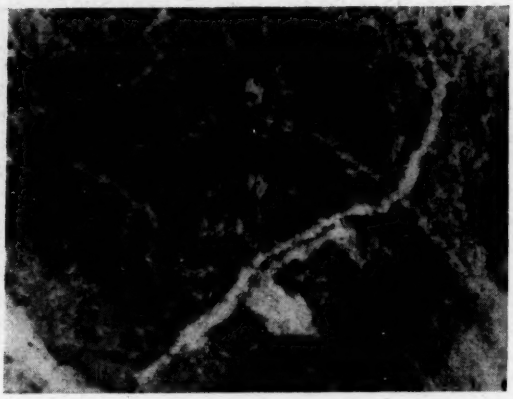

FIG. 1.

Hypertensive retinopathy. Retina in bulk. Haematoxylin. ×300 approx. Note the multitude of dilated capillaries (aneurysms). Hyaline thickening of vascular walls.

All calibre variations are sharply visible, spherical and spindle-shaped dilation stand out clearly (Fig. 1). They are of enormous frequency in different vascular retinal diseases.

Photomicros are unable so far to reproduce the fullness of the stereoscopic impression; sketches combining the images of different focus are more suitable.

Fatty changes of the vessel walls present a lively contrast shining red against the dark blue of the nuclei. Fatty aneurysms are frequent—they are convincing if we find them linked with a fatty capillary like a grape (Fig. 2). We found fatty aneurysms in diabetic eyes, sometimes with blood-filled dilatation of the venules, sometimes without "red" aneurysms. They are even more frequent in cases of thrombotic occlusion of the central vein. Sub-endothelial fatty necrosis is frequent as well, and is easily recognised in arteriosclerosis and atheromatosis, often found side by side in the same retina.

FIG. 2.

Diabetic and hypertensive retinopathy. ×600. Haemat. + Sudan IV. Fatty aneurysm in connection with fatty capillary.

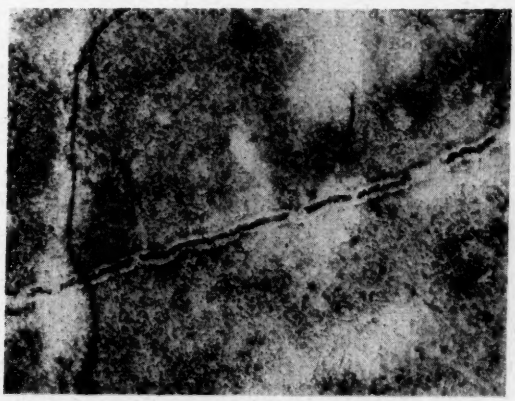

FIG. 3.

Diabetic + hypertensive retinopathy. Haemat. + Sudan IV. +150. Note the blood-filled vessel *a* with two fatty tributaries, (There are many others of the same type).

It is interesting to find that in some cases of hypertension a certain type of vessel exclusively is fatty (Fig. 3), neither the smaller of capillary size nor the bigger ones. I feel that the significance of this appearance needs explanation, which I have not found so far.

We recognise the fatty droplets in senile and degenerative ganglion cells (Loewenstein and MacGregor, 1943). The fat infiltration of the retinal ganglion cells in relatively young people (after thirty) is surprising and corresponds to similar changes in the brain substance. We are able to judge shape and position of fatty exudates and to decide definitely that the star-shaped exudate in the macular area is found in Henle's fibre layer.

If the specimen needs cutting we might decide to cut it with the fat reaction preserved, and we embed it, therefore, in gelatine, and section it with the freezing microtome, which makes serial investigation difficult.

No additional staining is necessary. Nuclear and fat staining show well in the section, or we embed in paraffin and section it serially, in which case, of course, there is no fat staining.

The technique of bulk investigation of choroidal tissue is similar. The hexagonal cells are so densely pigmented that they hinder the examination of the choriocapillaris. Depigmentation with potassium permanganate and oxalic acid must be carried out for a longer period than with sections. The retinal pigment is more resistant to oxydation than the branched chromatophores.

A very good view of the choriocapillaris is achieved by brushing off the hexagonal cells of their pigment content.

In such bulk specimens, stained with haematoxylin and eosin, I found in the lumen of the capillaries of the choriocapillaris large, prominent, endothelial cells, which might correspond to the "swell" cells I have described in the venules of the retina (Loewenstein, 1946).

Fatty sub-endothelial droplets in the vessels of the choriocapillaris are frequent. They are liable to escape routine examination. While investigating a considerable part of the choroid in bulk of hypertensive cases, I found only one or two bigger vessels with extensive fatty infiltrates, and the remaining choroid completely normal. I do not understand the significance of sclerotic changes of isolated choroidal arteries.

I found in different cases of uveitis studied in bulk and stained with haematoxylin—Sudan IV, masses of chromatophores filled with shining red droplets of different size, especially if the choroid has been placed outer layer upwards.

It seems that these branched chromatophores are reticulum cells which have phagocytosed fatty droplets. They mostly contain

besides fatty droplets, a granular light brown pigment. It seems that these reticulum cells have engulfed pigment granules produced by other pigment cells, the melanoblasts.

Summary

Double staining with haematoxylin and Sudan IV with clearing of the tissue, is recommended for bulk specimens of retina and choroid. It offers a better chance of discovering such vascular anomalies as pathological anastomoses, aneurysms, sub-endothelial necrosis, and exudates in the retina, especially if fat plays a part.

The method allows a careful study of the choriocapillaris and sometimes shows fatty changes in isolated choroidal vessels. The branched chromatophores in the outer choroidal layers are frequently filled with fat, in cases of uveitis, and they are considered to be phagocytic reticulum cells.

The technique recommended is very simple, and does not presume histological experience. Even a busy practitioner may learn to do the work unsupported by a technician.

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ANTERIOR FLAP SCLEROTOMY WITH BASAL IRIDENCLEISIS
(A Preliminary Note)

BY

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LONDON

RECENTLY I have tried a combined operation for glaucoma which I think possesses the merits of several of the accepted surgical procedures for this disorder. The operation consists in reflecting a conjunctival flap, fashioning a scleral flap hinged on the corneo-scleral junction, a limited cyclodialysis and the inclusion of a basal tongue of iris between the lips of the sclera leaving the sphincter pupillae intact. (See Fig. 1.) The results to date in 29 cases of chronic glaucoma and two of acute congestive glaucoma have been encouraging.

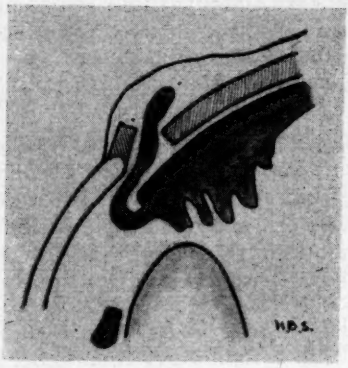

FIG. 1.

In all but one case satisfactory blebs have formed and remained, some are 6 mm. vertically and 8 mm. horizontally, and in all, the covering of conjunctiva and episcleral tissue has appeared to be substantial and in no instance thin and ectatic. (Fig. 2.) It seems on slit-lamp examination that the scleral flap is kept open on its hinges by the folded basal tongue of iris included in the lips of the

FIG. 2.

scleral incision. The intra-ocular pressure has fallen to 7-25 Hg mm. and remained so in 28 cases, and in these there has been no further field loss.

Miosis is produced before operation.

Anaesthesia. Pantocaine 1 per cent. and adrenalin. One ml. of novutox 3 per cent. with adrenaline 1/1,000 minims 2 is injected into the region of the ciliary ganglion and 0·5 ml. is injected into the belly of the superior rectus muscle. Pentothal and gas and oxygen may be given to nervous patients.

Operation. The speculum is inserted and a No. 1 white suture is passed through the tendon of the superior rectus muscle and clamped to the towel covering the frontal region. About 4 minims of novutox with adrenalin is injected beneath the conjunctiva about 3·5 mm. from the limbus from 10 to 2 o'clock so as to raise the episcleral tissues and conjunctiva.

The conjunctiva is now grasped and held forward by a pair of plane forceps 2·5 mm. anterior to the insertion of the superior rectus. The conjunctiva is snipped for about 5 mm. down to the sclera. Both blades of the spring scissors are then passed into the incision and directed temporally and downwards towards the limbus. (Fig. 3.) The blades are spread and the conjunctiva undermined. The closed blades of the spring scissors are next directed towards the nasal side and the limbus and are spread. The conjunctiva and episcleral tissues are thus undermined down to the limbus. The scissor blades are withdrawn. One blade of the scissors is then passed beneath the conjunctiva to the temporal side and slightly downwards and the conjunctiva is cut for

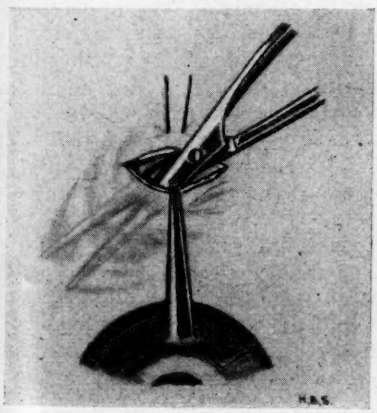

FIG. 3.

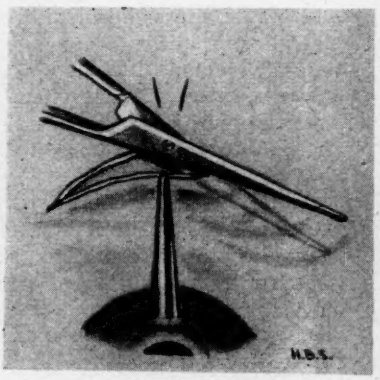

FIG. 4.

8 mm. or so from the mid-line. One blade of the spring scissors is then introduced beneath the conjunctiva on the nasal side and an incision 8 mm. or so in length is made towards the inner canthus and slightly downwards. (Fig. 4.) The conjunctival flap thus formed is turned forwards and downwards over the cornea and with a few brushing strokes from a small butter muslin swab the episcleral tissues are stripped cleanly from the sclera down to the limbus from 10 to 2 o'clock. With a double pronged conjunctival hook the conjunctival flap is held forwards and downwards by the assistant. In some cases a few strokes with Tooke's angled splitter will clear the episcleral tissue just above the limbus. Any bleeding points are checked by a touch from a heated probe. This probe also seals off any superficial episcleral vessels in the line of the scleral incision to be made 5 mm. long, 2 mm. above and concentric with the limbus.

A fine scleral hook is inserted into the sclera in the 12 o'clock meridian 2 mm. above the limbus. This steadies the eye during the scleral incision and it also retracts the anterior lip of the incision. (Fig. 5.)

The scleral incision is made with either a sclerotome or a ground-down cataract knife vertically in the sclera, that is at right angles to its surface and cleanly down to the ciliary body but not into this structure. The sclerotome has the advantage of guarded blade, the guard being set 1 mm. above the blade so that not too deep a cut is made. However, a small cataract knife used with care is very effective. When the ciliary body shows in the incision any remaining scleral fibres are divided by a few light strokes with the point of the cataract knife. (Fig. 5.) The scleral hook in the anterior lip of the scleral incision is now slightly raised and a cyclodialysis spatula is passed through the centre of the incision into the anterior end of the supra-choroidal lymph space, then on to separate the scleral spur and to enter the anterior chamber. When in the anterior chamber the spatula is moved in turn to each side of the scleral incision so as to effect a cyclodialysis 5 mm. long, that is the length of the incision. (Fig. 6.) Aqueous flows out of the incision during this procedure. The cyclodialysis spatula is withdrawn.

With the scleral hook still in place one blade of Westcott's scissors is passed on the flat into one end of the scleral incision for 2 mm. The blade is then rotated so that its cutting edge faces forwards and its blunt end is level with the corneo-scleral junction and 1 mm. nearer the mid-line than the end of the scleral incision. The blades of the scissors are closed and a converging cut is made in the sclera down to the limbus.

A similar procedure is done at the other end of the scleral incision

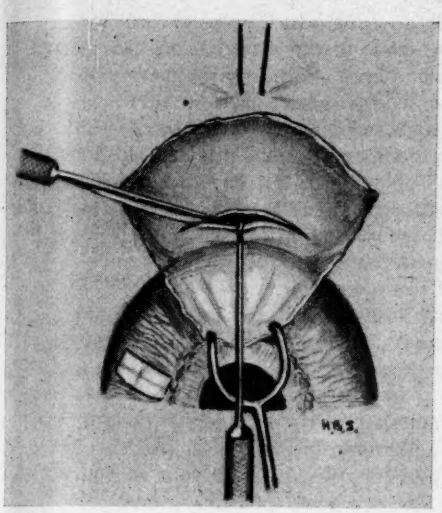

FIG. 5.

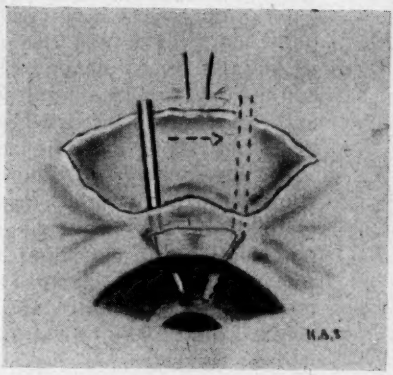

FIG. 6.

and when this is completed a hinged scleral flap is made based on the limbus. (Fig. 7.) The convergence of the lateral cuts towards the base of the scleral flap is, I am sure, important in maintaining the mobility of the flap on its hinge.

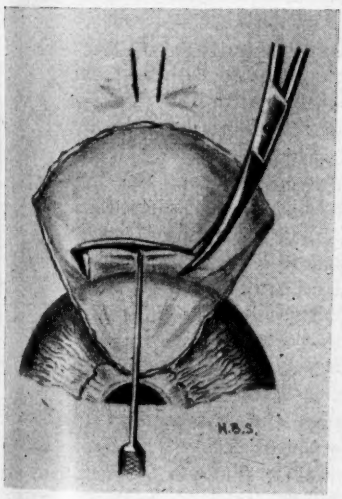

FIG. 7.

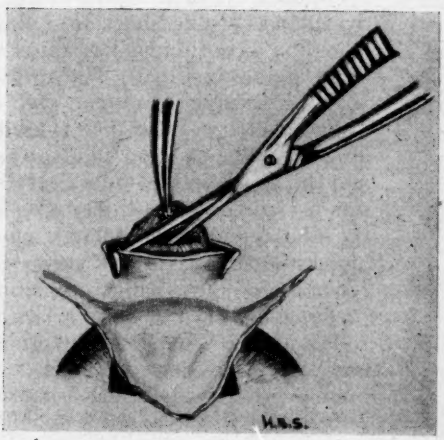

FIG. 8.

A pair of Lang's iris forceps is now introduced closed into the centre of the incision and, keeping close to the deep surface of the sclera is passed into the anterior chamber. Whilst this manoeuvre is taking place the assistant raises the conjunctival flap forwards and then upwards so that the progress of the iris forceps in the anterior chamber may be seen by the surgeon. 2·5 mm. above the pupil margin the iris forceps is opened for 2 mm. and the iris seized and drawn up into the centre of the scleral wound as the conjunctival flap is being drawn downwards by the assistant. Fine and smooth co-ordination between the surgeon and his assistant is necessary throughout this part of the operation.

A snip about 1·5 to 2 mm. long is made with fine blunt-ended spring scissors in the iris immediately in front of the forceps. One blade of the scissors is passed through the snip towards the temporal side and a cut about 3 mm. long is made towards the iris root. (Fig. 8.) A blade of the scissors is then directed through the iris incision nasally towards its root and a cut is made for about 3 mm. The folded tongue of iris based on its root is then laid on the sclera so that about 2·0—2·5 mm. projects above the upper lip of the scleral incision.

It may be necessary in some cases to replace the pupil by passing an iris repositor into each end of the scleral incision to the side of the basal tongue of iris included in the wound and with a gentle downward stroke towards the centre of the pupil to restore its circular contour. Often it is sufficient to apply an iris repositor to the upper part of the cornea and make a downward stroke over its surface.

Penicillin is instilled on to the exposed sclera and the conjunctival flap is stroked back into place. The conjunctival incision is closed by a continuous key pattern suture of 00 black silk. A drop of atropine is instilled. Tulle gras, a pad and bandage are applied.

Post-operative treatment and course. There is no need for digital massage. Atropine is used at the first dressing and omitted after this. The pad and bandage are left off 48 hours after operation and the eye protected by a Cartella shield. The patient is allowed into a chair on the 4th day after operation and leaves hospital on the 8th day. The scleral flap remains open and drainage of aqueous along the tongue of iris seems to be effective as judged by the reduction of intra-ocular pressure to within normal limits and the presence of a bleb which appears 8 to 10 days after operation.

The anterior chamber is reformed on the day after operation. In one case it was lost one week after operation but reformed in 48 hours. To-date there has been no anxiety about delayed or non-reformation of the anterior chamber. A small hyphaema 1-2 mm. deep occurred in 6 cases and caused no ill effect.

Iritis occurred 3 weeks after operation in one case but there was no sign of it in any other. In this respect the post-operative course differs from that of the trephine operation where some degree of iritis commonly occurs.

To-date there has been no case of choroidal detachment and no evidence that lens opacities have appeared or increased as a result of this operation.

It has been effective in two cases of acute congestive glaucoma.

ALLERGIC CONDITIONS OF THE EYE*†

1.—Keratitis Rosacea

BY

VERA B. WALKER

OXFORD

THE term " allergy " as used in the experimental section of this paper denotes an altered reaction rather than a hyper-sensitivity, as seen in the following example. Atropine in small doses, say one drop of 1/200 solution, dilates the pupil in 20 minutes, and in a slightly longer time causes immobilisation of the ciliary muscle and of the iris. In a few people, a much smaller dose, say 1/200,000, will produce this effect in 20 minutes, and we say they are *hypersensitive*. Occasionally we find that this smaller dose produces not only the expected reactions, but also oedema and irritation of the surrounding tissues, acute lacrymation, acute rhinitis and/or eczema of the eyelids. This is an allergic or altered reaction. In this sense one particular tissue, *e.g.*, conjunctiva, cornea or iris may be affected, and this is the usual finding; but occasionally several, and more rarely all, parts of the eye are involved simultaneously or successively.

Most allergic conditions are acute in onset and if recognised and treated at once clear up quickly, often within a few minutes or hours, leaving no permanent damage to the tissues involved. It is for this reason that this paper is entitled " Allergic Conditions of the Eye," rather than " Allergic Diseases," but it must be realised that once a tissue has remained in an abnormal physiological condition for some time, as in recurrent keratitis or iridocyclitis, there are secondary changes, due either to inflammation or to infection, which must be healed by routine treatment, though the

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† Received for publication, May 10, 1948.

allergist may be able to help in preventing a recurrence of the lesions.

We do not know why one tissue rather than another should be the " shock " tissue in any patient, and we are left wondering whether some damage, possibly congenital, and probably traumatic, must have been a forerunner of the condition. The presenting clinical signs and symptoms will depend upon the underlying structures of the various tissues involved.

In 1935 the Johns Hopkins Press published Woods' monograph on " Allergy and Immunity in Ophthalmology " in which the subject is presented from an immunologist's viewpoint, dealing with the relationship of allergy to focal infections, especially syphilis, tuberculosis and trachoma, but since that time recent work, especially in America, has shown that perhaps true allergy is rather a physiological or pharmacological abnormality, involving sensitised tissues and wet mucous membranes. In those conditions in which an infection is proved, this infection is secondary to the allergic diathesis. It will be seen from the case-sheets quoted below, that a most important point in diagnosis is an accurate family history, for almost without exception the patient has other allergic manifestations, or some of his relatives have asthma, urticaria, hay-fever or migraine.

During the last ten years many distinguished workers have written about the antigen-antibody reaction, which gives rise to the allergic reaction. Bothman[1] (1941) describes an allergic reaction as " an antigen-antibody reaction freeing a histamine-like substance which leads to capillary dilatation, increased permeability of vessel walls, and an exudation of serum which contains toxic substances." The earlier work was ably summarised by Duggan[3] (1946). He is an ophthalmologist, who, after working for some years in the Department of Physiology at the College of Physicians and Surgeons, Columbia University, stated that " To me, allergy includes all those aseptic and abacterial lesions in which the basic pathological process can be reduced to a common denominator of either increased capillary permeability or excessive contraction (spasm) of smooth muscle, or both . . . since except for the muscles of the iris and the ciliary body, most of the smooth muscle of the eye is found in the walls of the arteries and arterioles. I think that allergy of the eye can be interpreted as a problem in vascular physiology."

Whether the accumulation of histamine, due to exogenous or endogenous allergens, and the effect of that histamine on the smooth muscle of the body is a whole explanation of the changes seen, or only part of it, still remains uncertain, although Duggan's interpretation seems to offer a satisfactory explanation of most, if

TABLE I

Presenting pathology	Approximate per cent. of cases which can be proved to be allergic
Angioneurotic oedema	70
Blepharitis	10+
Conjunctivitis	40+
Keratitis	10
Keratitis rosacea	70
Iritis	3
Iridocyclitis	2·5
Glaucoma	5
Retinal haemorrhage or detachment	1
Choroiditis	3
Cataract	0·2
Migraine	54

not all, of the conditions seen in the various tissues of the eye. Depending on which tissue is sensitised to the offending allergen—*i.e.*, the " shock " tissue—we may see angioneurotic oedema, blepharitis, conjunctivitis, keratitis, iritis, iridocyclitis, keratitis rosacea, retinal haemorrhage or detachment, choroiditis, glaucoma, cataract or migraine. From Table I it will be seen that some of these conditions are frequently allergic, and some only occasionally so. Tables II and III show that in keratitis rosacea, 70 per cent. of the cases can be satisfactorily investigated and treated by desensitisation.

Keratitis rosacea

Rosacea, a relatively common abnormality of the skin of the face of adults between the ages of 20 and 50 years, is frequently accompanied by ocular manifestations, varying in degree from a mild conjunctivitis, through all the stages of blepharo-conjunctivitis, episcleritis and keratitis, to eventual visual incapacity. It is all too frequent to find the patient, and sometimes his doctor, too, confident that each recurrence will be less severe, and that he will " grow out of it " when aged 50. If possible before marginal vascular infiltration shows that the cornea is involved, and whether accompanied by an exacerbation of facial acne or not, a note of warning should be given. Numerous as the list of possible causes of keratitis rosacea may be, almost all authors agree that the condition is " a metabolic, rather than a local one"; digestive

upsets (Ryle and Barber,[8] 1920; Brown,[2] 1925; Eastwood,[4] 1928, 1934), deficiency diseases (Johnson and Eckardt,[7] 1940; Sydenstricker, Sebrell, Cleckley and Kruse,[10] 1940; Johnson,[6] 1941; Fish,[5] 1943), and hormonal disorders (Zondek, Landau and Bromberg,[12] 1947), all play a part, and must be treated appropriately, but even after all these have been corrected, and all bacteria removed, there is still an underlying condition which predisposes to recurrence. From a survey of the 76 cases in Tables II and III it will be seen that allergy plays a fundamental part in the syndrome :—

TABLE II

Total number of cases investigated, all with skin lesions ...	76
With conjunctivitis or blepharitis, but not yet keratitis ...	26
First atack of keratitis, 13 Recurrences - - 37 }	50

		Specific allergens found
Family history of allergy	56	43
Induced allergy after measles, or other high temperature disease	7	5
After "protein-shock" therapy ...	2	1
No explanation of allergy	11	3
	76	52=70%
Allergy not *proved* in	24	

TREATMENT

Local (1) Removal of secondary infection with pen. ung., sulphathiazole, Dettol, or other disinfectant;

(2) Application of a dithranol* (0·1 per cent.) cream to the skin b.d. for at least two weeks;

General. Desensitisation of the 52 with specific antigens by a six-weeks' course of injections;

Non-specific desensitisation of the other 24 with *Histamine-azo-globulin*, by 10 graded intramuscular injections (0·05 c.c., 0·1 c.c., 0.2 c.c., 0.3 c.c., 0·4 c.c., 0·5 c.c., 0·6 c.c., 0·7 c.c., 0·8 c.c., 1·0 c.c.) at the rate of two injections a week for 5 consecutive weeks.

If at a later date a recurrence of symtoms of either eye or face occurs, then give 0·5 c.c. histamine-azo-globulin immediately, and repeat after four days.

* dithranol = dihydroxy-anthranol.

TABLE III

Group A = Specific allergens found (*see* Table II).
Group B = Specific allergens not found.

Year	No. of cases investigated	Recurrence in six months	Recurrence in two years
A			
1942	6	2	3
1943	9	1	2
1944	9	2	2
1945	10	1	3
1946	8	0	1
1947	10	2	–
	52	8	11/42=25%
B			
1945	2	0	1
1946	12	2	5
1947	10	3	–
	24	5	6/14=43%

$\frac{11+6}{42+14}$ = 39/56 = 70 per cent. symptom-free for 2 years (both face and cornea).

The 20 cases treated in 1947 are not included in this percentage, as two years have not elapsed since completion of their treatment.

From these tables it can be seen that 70 per cent. of the patients with keratitis rosacea have not had a recurrence of symptoms within the two years following their treatment; many of these 70 per cent. are still symptom-free after three, four or five years.

There is, however, a significant difference between Group A, in which specific allergens were found, and Group B, in which all were treated with histamine. In Group A, the percentage remaining symptom-free was nearly twice as great as in Group B.

I would like to emphasise the urgency of referring all cases of keratitis rosacea to the allergists for investigation; and indeed other patients with keratitis of unknown origin, especially those with a family history of acne, eczema or urticaria, even though their own skin manifestations have not yet become obvious.

Summary

An analysis of 76 cases of keratitis rosacea is presented. In 52 of them an allergic cause for both the skin and corneal lesions has been found.

After desensitisation, 70 per cent. of cases remained symptom-free for at least 2 years.

I take this opportunity of expressing to my colleagues at the Oxford Eye Hospital and at the Horton General Hospital, Banbury, my appreciation of their generous co-operation in this investigation; also of thanking Messrs. Parke, Davis Ltd. for supplies of histamine-azo-globulin used for 24 patients.

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ALLERGIC CONDITIONS OF THE EYE*†

2.—Migraine

BY

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OXFORD

MIGRAINE is of importance to ophthalmologists, *first* because all humans with severe headaches, from whatever cause, eventually find their way to an eye hospital to be checked for refraction errors, and *second* because 50 per cent. of migraine cases have eye symptoms, often very severe in onset.

As early as 1820 some French authors were classifying migraine with epilepsy, eczema and asthma as manifestations of allergy, but Strümpell[4] (1860) was the first to suggest an allergic basis for some cases of migraine, and he spoke of it as "an exudative process comparable to urticaria and angio-neurotic oedema." Liveing's[2] (1873) monograph "On megrim" is a classical work on the subject.

In the 20th century many papers have been written quoting cases of migraine attacks in patients who gave positive skin reactions

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†Received for publication, May 10, 1948.

with certain foods or inhalants, but there has been a noticeable hesitation to claim a direct connection between the symptoms and signs. Perhaps one of the difficulties of any argument on the subject is the fact that migraine attacks usually occur in the healthiest of patients, sudden in onset, and leaving no trace of pathological abnormality when the attack is over, whether it has lasted one hour or twelve. This difficulty can be overcome if we consider allergy as a physiological, rather than a pathological response, differing from the normal in degree but not in kind.

In the 1935 Edition of Osler's[3] text-book, migraine is defined as "A paroxysmal affection characterized by severe headache, usually unilateral, and often associated with vomiting and/or disorders of vision." Numerous subsequent writers have elaborated this to suit individual patients or groups of patients. All cases classified as migraine in the following tables satisfy this definition.

In 100 consecutive cases of such migraine investigated in 1943-47, 54 were proved to be allergic, either by clinical trials, by skin tests, or, more often, by both methods. With each patient an attempt was made to produce a migraine attack, before prophylactic treatment was begun.

Typical examples of these patients were :—

CASE 1. Patient, male, aged 52 years. 115/75. C/o migraine + neuralgia. Duration : 8 years (about 50 attacks a year). F.H. : Asthma and migraine.

Positive allergies by skin test : Feathers +++, Dust +++, Cat +.

Allergies confirmed by clinical trial : feathers and dust. Treatment : desensitisation. Attacks in next 6 months, 0; attacks in next 3 years, 1.

CASE 2. Patient, female, aged 48 years. 110/80. C/o migraine. Duration : 20 years (resigned position as secretary owing to frequency of migraine). F.H. : Migraine.

Positive allergies by skin test : House dust +++, Kapoc ++.

Allergies confirmed by clinical trial : house dust, kapoc. Treatment : desensitisation. Attacks in next 6 months, 2; attacks in next 5 years, 12.

CASE 3. Patient, male, aged 8½ years. 90/60. C/o migraine + urticaria. Duration : 4 years, in summer only. F.H. : Hay-fever and urticaria.

Positive allergies by skin test : Timothy grass +++. Allergy confirmed by clinical trial : Timothy grass. Treatment : Desensitisation. Attacks in next summer, 0; attacks in next 3 years, 0.

CASE 4. Patient, female, aged 53 years. 121/90. C/o migraine + eczema. Duration : 25 years (irregular—usually 3 in a month). Worse in last three years. F.H. : None reported.

Positive allergies by skin test: Cheese +++, Peas ++, Beans ++.

Allergies confirmed by clinical trial: cheese, haricot beans. Treatment: avoidance. Attacks in next 6 months, 0; attacks in next 6 years, 3.

CASE 5. Patient, female, aged 42 years. 115/80. C/o migraine. Duration: 15 years (at least once a week). F.H.: Migraine.

Positive allergies by skin test: House dust +++, Kapoc ++.

Allergies confirmed by clinical trial: house dust. Treatment: with extracted dust from own house. Attacks in next 6 months, 0; attacks in next 5 years, 1.

CASE 6. Patient, male, aged 10 years. C/o sickness and dull headaches (" half-headaches "). Duration: 2 years. Missed 31 days at school in 1 term. F.H.: Migraine and asthma.

Positive allergies by skin test: Cat +, Dog +, Fish +, Chocolate ++, Milk ++.

Allergies confirmed by clinical trial: chocolate, cod liver oil, whole milk (unboiled). Treatment: Avoidance. Days absent from school in next term, 2; days absent from school in next 6 terms, 3.

While these cases show that *if* a patient has *allergic* migraine, he can be helped tremendously by avoiding those allergens to which he is specifically sensitive, or by being desensitised, we must remember that the other 46 per cent. should be excluded from these somewhat tedious investigations, as they can derive no benefit from them. They do not belong to allergic families, and they do not present other manifestations of allergy themselves.

Realising that all patients are reluctant to give a detailed family history or an accurate personal history, other more clinical methods

TABLE I

Migraine in 100 consecutive *adult* cases

No.	Average age	Systolic pressure	Allergic origin	Per cent.
8	45	150—180	0	0
20	43	130—150	8	4
10	44	120—130	3	30
45	43	100—120	28	62
17	40	>100	15	88
100	43	—	54	—

Average for 46 non-allergic cases - - *147*

Average for the 54 allergic ones - - *108*

for separating the 54 per cent. allergic from the 46 per cent. non-allergic patients have been sought, and during routine general examinations significant differences of systolic blood pressures in the two groups were observed; there was no marked difference in pulse pressures.

These were all adult cases, and the pressures were all taken *between*, rather than *during* attacks. Bray[1] (1937) stated that in children he had not found any marked changes in the blood pressure during allergic attacks. Witts[5] (1933) determined the blood pressure in 440 cases of asthma, and found that the majority showed normal figures, but he did not separate the allergic asthmas from those due to other causes. From Table I it becomes clear that although *all* migraine cases do not have low systolic pressures, and all migraines are not of allergic origin, if a patient with true migraine has a low systolic pressure, then allergy should be suspected and treated appropriately.

In conclusion, attention is drawn to the apparent increase in the number of allergic patients in any community during the last two decades. They are presenting as asthmas, eczemas, conjunctivitis cases, migraines or urticarias to our general practitioners all over the country. Perhaps this increase is apparent only: it may be that many minor cases of *sub-clinical* allergy, have by the stress of present-day conditions, both mental and physical, become major cases, seeking the help of their medical advisers, and that the actual number remains fairly constant from generation to generation. Many patients seeking advice to-day for incapacitating migraine give a history of "mild half-headaches" in 1938, or even in 1928.

Summary

(1) An analysis of 100 cases of migraine is given. Fifty-four of them were proved to be of allergic origin, and remained free from head pain after desensitisation, or avoidance of their allergens.

(2) The average systolic blood pressure of the fifty-four allergic cases was noticeably lower than that of the forty-six non-allergic ones.

(3) It is concluded that migraines in patients with a *low* systolic pressure are manifestations of allergy.

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THE EFFECTS OF VARIOUS TYPES OF PENICILLIN INJECTED INTO THE VITREOUS*

BY

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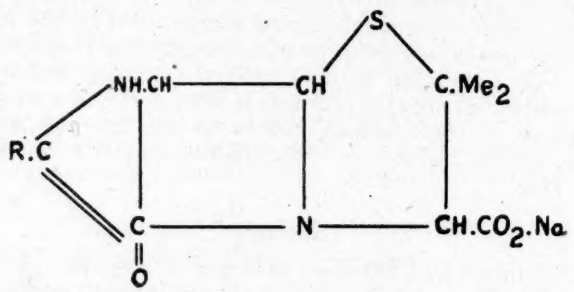
IN a previous study (Duguid *et al.*, 1947) it was found that a solution of pure crystalline penicillin could be injected into the vitreous of rabbits, without producing any marked injury, the toxic effect being indeed much smaller than those resulting from the injection of impure preparations of the drug. Penicillin did, however, cause small areas of retinal damage in some cases. It is now known that such a pure preparation of penicillin is not a single compound but consists of at least five different compounds all similar in composition, but differing in the nature of one chemical group, viz., R. in the formula shown below :—



The different penicillins are Penicillin I (or F according to the American nomenclature), in which R is 2—pentenyl; Penicillin II (G), in which R = benzyl; Penicillin III (X), in which R = p-hydroxy-benzyl; Penicillin IV (K), in which R = n-heptyl; and dihydro-penicillin I, in which R = n-amyl. The properties of these penicillins show appreciable differences and it seemed possible that one of them might be more suitable than the others for intravitreous injection, either because it is less toxic, or diffuses away more slowly or both. Thanks to the generous supply of these substances by the Antibiotics Study Section of the U.S. Public Health Service (through Dr. Seger) we were able to undertake an

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investigation of these questions and the results are given in the present communication.

Methods

The penicillins were dissolved in sterile saline and injected into the vitreous by the same method used previously (Duguid *et al.*, 1947). The dose introduced was 1·2 mg. or 3·0 mg. in 0·1 ml. saline. In each case the injection of penicillin was made into the vitreous of the right eye, while 0·1 ml. of saline was introduced into the vitreous of the left eye which was then used to control the clinical and histological findings in the right eye. For comparison experiments were also performed with a pure mixed penicillin (Glaxo) and the dose was 2,000 units or 5,000 units which has practically the same activity as 1·2 mg. and 3·0 mg. of penicillin II (G). The eyes, including the fundi, were always examined before the injection. The eyes were observed for periods varying from 10 to 128 days following the injections, particular attention being paid to the fundi and media. Finally the eyes were removed for histological examination. The globes were bisected in front of the ora serrata and the posterior portion examined with the help of a loupe or the slit-lamp in order to identify ophthalmoscopic changes. Portions of the posterior globe were embedded in paraffin and stained with haemalum and eosin. In view of previous findings with retinal tissue exposed to penicillin (Duguid *et al.*, 1947), and the primary intention of the experiment being to compare the different penicillins, it was not considered necessary to use further staining methods.

In the experiments on diffusion the drugs were introduced into the vitreous in the same way; 1·2 mg. in 0·1 ml. saline of penicillins G, X and K were injected into the vitreous and the animals killed after intervals of 24 and 48 hours. Samples of aqueous and vitreous were taken immediately with the eyes still *in situ*. The eyes were then removed, dissected under aseptic conditions, and samples of cornea, sclera, iris and ciliary body removed, dried on sterile blotting paper and each added to a Bijou bottle of known weight and weighed. Extraction of penicillin from the tissues by grinding in an agate mortar with sand and saline or by leaving the tissues in 0·5 ml. of saline at 4° C. overnight were tried. The latter process gave the more consistent results and was finally adopted throughout.

The penicillin estimations were made by a serial dilution method using a glucose-serum water medium with phenol red as indicator. The volume of eye fluid extract for testing was either 0·2 ml. or 0·4 ml. The Oxford staph. aureus H was the test organism and

the end point was read as the highest dilution of test fluid completely inhibiting growth of the organism, as indicated by failure to alter phenol red from red to yellow. A 1/200 dilution of an 18 hour culture of staph. aureus in glucose serum water was inoculated into each tube.

The eye fluids or saline extracts from animals not receiving penicillin were not found to have any bacteriostatic activity.

Section 1.—The effects of the drugs on the eye

The results detailed below are based on histological and ophthalmoscopic examinations of the eyes. In some cases histological changes are present, although the clinical findings before enucleation were normal, a finding already noted by Duguid *et al.* (1947). The initial stages of the clinical changes observed ophthalmoscopically were very similar whatever the type of penicillin used. Within 48 hours of injection a certain degree of oedema was seen in some part of the inferior retina not in relation to the site of the injection which was in the upper part of the eye. A peak of oedema was rapidly reached and within 10 days it began to subside. When this oedema was very slight the retina then frequently appeared to be normal and remained so. In some cases the oedema did not disappear. Persisting fine pigment changes became visible in most of the eyes as the oedema subsided or in some cases after a latent interval.

Refractile particles similar to a localised synchisis appeared in the vitreous in a few of the rabbits injected with F, X and G. These settled on the floor of the retina after some weeks and then took on the appearance of small, hard, white particles. In most cases they were few enough to be counted, varying between 12 and about 50.

Penicillin K showed a peculiarity in that it produced new vessel formation when given in sufficient dosage.

Mixed penicillin (pure).—Mixed penicillin injections were given intravitreously to six animals in dosages of 2,000 and 5,000 units. The periods of observation following injection were 53 to 79 days.

Of those animals which received the smaller dose one showed retinal changes affecting the rod and cone layer over a limited area above while two showed some vacuolation of the nerve fibre layer, due possibly to oedema. Clinically no changes were noted in the retina in these cases.

Of the animals which received the larger dose, one showed an area of disturbance of the outer retinal elements. This was in keeping with the clinical appearances.

The findings in these cases are confirmatory of previous descriptions of the retina following the injection of pure mixed penicillin

(Sallmann *et al.*, 1944 ; Duguid *et al.*, 1947). It is of interest that there would appear to be no delayed effect of penicillin on the retina as the periods of observation were 53-79 days in the present series and 10-27 days in the series reported by Duguid *et al.*

Penicillin II (G).—Altogether 12 animals were treated with penicillin G and observed over a period of from 42-117 days. In the six eyes which received 1·2 mg. of the penicillin, no histological changes were noted other than, in one eye, the presence of a delicate non-cellular exudate lying on the surface of the retina. In two of the eyes, however, there were slight changes noted clinically. These consisted of pigmentary and atrophic changes in the anterior inferior quadrant of the fundus. It would appear that the sections do not include the affected areas in these two eyes and the histological changes can be assumed to be similar to those found in two eyes which received 3·0 mg. of the penicillin as now described. Six eyes received 3·0 mg. of the penicillin. Two showed a disturbance or loss of the outer retinal elements over a limited area. In one of these eyes there was a proliferation of pigment into the disturbed retina.

Penicillin III (X).—Five animals were treated with penicillin X in doses of 1·2 and 3·0 mg. and observed over a period of 50-93 days. In the two eyes which received the smaller dose no abnormality was detected in the retina. Of the three eyes which received the larger dose, two showed disturbances and loss of the outer retinal elements over fairly extensive areas with pigment migration into the retina in one of the eyes. The remaining eye of those receiving the larger dose showed non-cellular vitreous changes overlying areas of choroidal disturbance.

Penicillin I (F).—Seven animals were treated with penicillin F in doses of 1·2 and 3·0 mg. The periods of observation were 21 to 128 days. In the three eyes which received the smaller dose no gross retinal changes were observed but one showed changes in the internal limiting membrane of the retina which had a " blistered " appearance. Of the four eyes which received the larger dose, only one showed a normal retina. Of the others, two showed extensive areas of disturbance or loss of all the retinal elements with pigment migration while in one the changes were limited to a disturbance of the outer retinal elements.

Dihydro penicillin F.—Six eyes were treated with dihydro penicillin F in dosages of 1·2 or 3·0 mg. The periods of observation were 10 to 106 days. Of the three eyes which received the smaller dose, two showed areas of disturbances or loss of the outer retinal elements. Of the three eyes which received the larger dose, two showed areas with loss of the outer retinal elements, while one showed extensive destruction of all retinal elements with gross pigment infiltration of the retina.

Penicillin IV (K).—Five eyes were treated with penicillin K in doses of 1·2 and 3·0 mg. and observed over periods varying from 56-92 days. Of the three eyes which received the smaller dose, two showed disturbance and loss of all the retinal elements over certain areas and one of these eyes showed pigment migration into the retina. The eye which showed no retinal changes had an opacity of the lens. The two eyes which received the larger dose of penicillin K showed very extensive areas of gross destruction and atrophy of the retina with the formation of new vessels in the vitreous.

Summary of effects of various types of penicillin on the retina

A study of these forty-one eyes shows :—

(*a*) All the various types of penicillin as well as mixed penicillin are capable of producing a toxic effect on the retinal cells.

(*b*) The changes produced are similar in kind with all the types of penicillin, excepting that only with penicillin K was new vessel formation produced. The changes consisted of localised patches of retinal destruction, the initial effect being on the outer retinal elements especially on the layer of rods and cones. In only one eye was the choroid found to be affected.

(*c*) The degree of change varied with the amount of penicillin introduced into the vitreous.

(*d*) The degree of change also varied with the type of penicillin used. In Table I the various types of penicillin are arranged in order of their increasing toxicity.

It can be seen that the toxic effects of mixed penicillin and of penicillin II (G) are the same and that both are the least toxic of the different types.

Section 2.—The diffusion of the drugs within the eye

The diffusion of mixed penicillin when it is introduced into the vitreous has already been described (Duguid *et al.*, 1947). These authors determined the concentrations of penicillin found in the vitreous, aqueous and cornea, one hour, six hours, one day, two days, and three days after the injection of mixed sodium penicillin into the vitreous. Chemotherapeutic concentrations (*i.e.*, about 1/20 of a unit per ml.) were maintained in the vitreous for 2-3 days, and in the aqueous and cornea for 1-2 days. In the present experiments the concentration of penicillins G, X and K were tested in the vitreous, aqueous, cornea, sclera and ciliary body, 24 and 48 hours after the injection of 1·2 mg. into the vitreous and the results are shown in Table II and Fig. 1. These two testing periods were

TABLE I

	No. of eyes observed clinically and histologically	No. of eyes showing no change	No. of eyes showing loss and disturbance of outer retinal elements only	No. of eyes showing loss and disturbance of all retinal elements
		All expressed as a fraction of the number of eyes examined		
Mixed penicillin (pure)	6	4/6	2/6	0/6
Penicillin II. (G)	12	8/12	4/12	0/12
Penicillin III. (X)	5	2/5	3/5	0/5
Penicillin I (F)	7	4/7	1/7	2/7
Penicillin Dihydro I (F)	6	1/6	4/6	1/6
Penicillin IV (K)	5	1/5	—	4/5

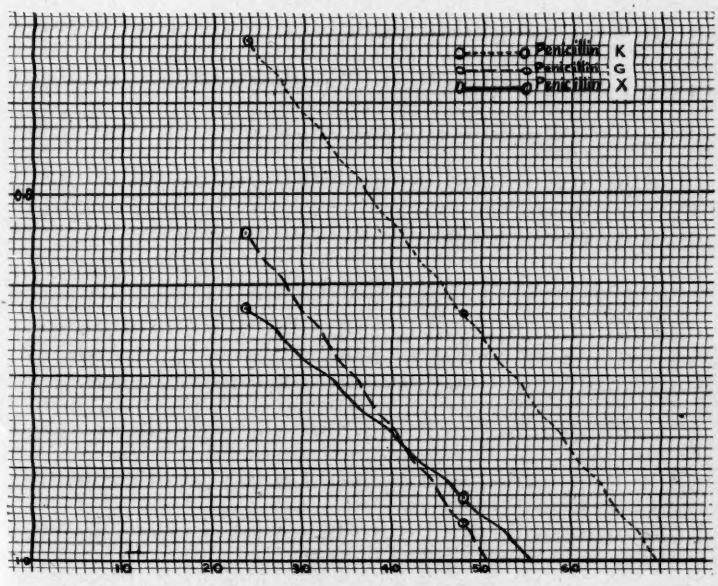

FIG. 1.

Persistence of penicillins G, K and X in the aqueous following the intra-vitreous injection of 1·2 mg. of the penicillins.

TABLE II—*Concentrations of penicillins after intra-vitreous injections (1·2 mg.)*

Type of penicillin	Rabbits' Number	Concentration of penicillin (U/ml.).				Concentration of penicillin (U/g.).		
		24 hours R.E.		48 hours L.E.		at 24 hours		
		Vitreous	Aqueous	Vitreous	Aqueous	Cornea	Sclera	Ciliary Body
G	64 R.E.	80	$\frac{1}{2}$	—	—	4·5	4·0	3·4
	64 L.E.	80	$\frac{1}{2}$	—	—	2·0	6·0	4·5
	74	20	$< \frac{1}{8}$	$\frac{1}{2}$	$< \frac{1}{8}$	—	3·85	2·8
	75	20—40	1·0	$\frac{1}{2}$	$< \frac{1}{8}$	3·0	3·0	4·9
	19	40	2·0	1·0	$\frac{1}{8}$	2·9	5·0	6·5
	94	40	1·0	$\frac{1}{4}$	$< \frac{1}{8}$	2·8	8·3	8·0
X	93	80	$< \frac{1}{8}$	1	$\frac{1}{8}$	—	5·57	3·8
	95	40	$< \frac{1}{8}$	$\frac{1}{2}$—1	$< \frac{1}{8}$	—	3·2	5·1
	60	80	$\frac{1}{2}$—1·0	2·0	$\frac{1}{8}$	3·0	15·4	5·1
	61	40	$\frac{1}{2}$	1—2	$\frac{1}{8}$	5·5	8·1	4·6
	97	20—40	$< \frac{1}{8}$	1·0	$\frac{1}{8}$	1·5	5·0	4·4
	98	40—80	$\frac{1}{2}$	2·0	$\frac{1}{4}$	2·2	5·3	7·0
K	72	20	1·0	2·0	$\frac{1}{2}$	—	2·1	5·7
	113	10	1·0	2·0	$\frac{1}{2}$	—	—	—
	144	10	$\frac{1}{2}$	$\frac{1}{2}$—1	$< \frac{1}{8}$	2·3	—	—
	145	40	1·0	2·0	$< \frac{1}{8}$	2·8	1·2	3·0—6·0
	152	160	> 4	2·0	$\frac{1}{2}$	3·9	> 10·6	—
	153	10—20	1·0	1·0	$\frac{1}{2}$	5·8	3·7	—

considered sufficient for the purpose of determining whether there was any difference in the diffusion rates of different types of penicillin. It can be seen that there is no material difference in these rates of diffusion, although penicillin K diffuses rather more slowly. This is interesting since penicillin K is less stable than penicillin G and X when given systemically. (Coghill *et al.*, 1946.)

Discussion

There would appear to be little doubt that penicillin K and F are the most toxic, and that mixed penicillin and penicillin G are the least toxic on the retina. In view of this it is unexpected that the toxic effects of mixed penicillin and penicillin G are the same in the eyes examined. If the eight eyes examined histologically following the injection of mixed penicillin, as reported by Duguid *et al.* (1947), are added to the present series, a comparison between the effects of mixed penicillin and penicillin G is as follows:—

	Number of eyes examined histologically	Number of eyes showing retinal degeneration
Mixed penicillin ...	14	5
Penicillin G	12	4

In view of these results it is probable that the mixed penicillin used in these experiments contained only small amounts of penicillins X, F and K. Unless it can be certain that a pure mixed penicillin does essentially consist of penicillin G, it would be preferable to use a pure preparation of penicillin G for intra-ocular administration, and this is in fact now available.

Summary

(1) The toxic effects of pure mixed penicillin and penicillins G, X, F, K and dihydro F on the retina when introduced into the vitreous are compared. It is found that penicillin G and mixed penicillin are the least toxic.

(2) The diffusion rates of penicillin G, X and K when introduced into the vitreous are compared. The diffusion rates are similar and found to be comparable to those of mixed penicillin.

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HERNIA AND PROLAPSE OF THE VITREOUS AND PROLAPSE OF THE IRIS IN CONNECTION WITH THE CATARACT OPERATION

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AT the operation for cataract the iris is usually replaced with the spatula and the wound closed definitely. Although this is, as a rule, so simple, we know that there are very often cases where difficulties arise in the reposition of the iris. This question will be discussed here on the basis of some of my earlier studies later extended.

From Dejean's and especially Ida Mann's investigations we know that when the human embryo is 1 cm. in length, the arteria hyaloidea and the veins surrounding it pass conically from behind to the front, to the posterior surface of the lens. These veins, together with the fibres between them, form the primary vitreous. Around it the retina soon grows the secondary vitreous. To illustrate the conditions at the time of birth I have compared the primary vitreous with the old-fashioned stethoscope, the smaller end being on the papilla, the tube passing horizontally from behind forward, and the larger end being on the posterior surface of the lens. What is inside the stethoscope belongs to the primary vitreous, and what is around it to the avascular, more solid secondary vitreous. The walls of the stethoscope then form the intervening membrane between these two parts of the vitreous.

During the first four years the tube of the stethoscope as it were sinks deeper and becomes obliterated. Thus there arises a practically vertical posterior wall to the primary vitreous separating it from the secondary vitreous behind.

Whoever examines the front parts of the vitreous in the optic section of the slit-lamp will observe that immediately behind the lens an optically empty narrow space begins. Koeppe called it the post-lenticular and Vogt the retro-lental space. According to the latter, it contains aqueous humour.

Inspired by an observation made by Comberg I have, as I think, proved that such a post-lenticular or retro-lental space does not exist. Omitting explanations, when I removed the cornea and the lens from an enucleated human eye or that of certain animals and then studied the front parts of the vitreous, now exposed to the open air, with the aid of a slit-lamp, this so-called retro-lental space

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was as visible as in an untouched eye, and when I examined eyes after intracapsular lens extraction the space of Koeppe and Vogt was also seen in all of them. Thus the space behind the lens that appears empty really belongs to the vitreous. It is the residual part of the primary vitreous and therefore I have suggested for it the name " primary space."

The membrane where the vitreous was believed to begin is in point of fact within the vitreous. It is the border between the primary and the secondary vitreous and consequently may be called intervening membrane. The practical importance of these questions will be reverted to later, but first, what happens to the front surface of the vitreous during and after the extraction of the lens from the eye?

If we remove totally the cornea and the lens from the eye of a human or a pig we see that the smooth surface of the vitreous is really covered by a very thin membrane which can be grasped with capsule forceps and, to some extent, folded, even if it is more fragile than the lens capsule. If a cut is made on the front surface of the vitreous its edges form lighter folds and, if the eye is then slightly pressed, the vitreous begins to emerge from the wound. To bring out more vitreous the pressure should be slightly increased probably due to the fact that the thinner primary vitreous escapes first, and when the intervening membrane is broken, the more solid secondary vitreous. However, it is not always possible to notice such a difference.

It is known that the front surface of the vitreous after the cataract operation tends to be pushed into the anterior chamber. But the size and form of the distention varies greatly, especially according to whether the extraction has been extra- or intracapsular. Particularly after intracapsular extraction of the lens the front surface

FIG. 1.

About ¼ of the cases (no hernia at all).

FIGS. 2 and 3.

The commonest types.

FIG. 4.

About 10 per cent. of the cases.

FIG, 5.

Front membrane partially perforated.

FIG. 6.

Front membrane largely ruptured. The vitreous fills the whole anterior chamber and makes it deep.

of the vitreous tends to be pushed into the anterior chamber in the shape of the head of a fungus, forming a kind of hernia. There were two kinds of hernias. I have called the one with an intact surface membrane simple, and the others complicated (Figs. 1—6).

No hernia has occurred after intracapsular cataract extraction in about ¼ of recent cases. In nearly 10 per cent., on the other hand, the hernia is so high that it reaches the posterior surface of the cornea. The lower hernias are between these limits. If iridectomy has been performed the hernia is, as a rule, slightly higher.

The complicated largest hernias have, of course, no surface membrane and the vitreous flows into the anterior chamber which is then generally exceptionally deep.

Proceeding to study the prolapse of the iris and the vitreous, it seems advisable to deal first with the so-called semi-prolapse or the danger of prolapse, *i.e.*, the pupil drawn up towards the incision. Among such cases the cause of this updrawal of the pupil is surprisingly often the fact that there are some residual fine fibres of the embryonic pupillary membrane and these fibres—overlooked at the routine examination—stretch and wedge themselves into the wound at the extraction. Other causes are the torsion of the broken, or even unbroken, front membrane of the vitreous around the pupillary margin, and the wedging of this membrane into the wound. Such cases, I believe, occur more frequently after tumbling extractions. Drawing up of the pupil may be due also to other causes.

Though prolapse of the iris and of the vitreous are not inseparable Siamese twins, they are so closely connected that we can say: where the one is, there the other is on the way—corpus ante portas!

Here the general precautionary measures which have been invaluable to cataract patients will be omitted; a previously laid corneo-scleral suture must probably now be included among them. At our clinic the incision is closed after extracting the lens with a triangle suture (Vannas[2]), but the threads are not yet tied. Instillation of eserine which de Wecker introduced as long ago as 1886 is a very valuable aid which has an immediate effect. The use of eserine to straighten the columns of the iris is indicated also in cases where iridectomy has been performed.

In any extensive series of operations, we can distinguish the following different groups: 1. Miosis occurs already after the first instillation of eserine. 2. The pupil does not contract even after many instillations, although the pupil moved normally before the operation. What is the cause of this difference?

The explanation is probably to be seen in Figs. 1-6. There is a hernia of the vitreous in the anterior chamber.

If the hernia is simple and shallow the pupillary margin easily

glides along the surface of the vitreous and the result is miosis. With a hernia of medium height the result is + or −. In high hernias the stem of the fungus can narrow but the head remains in the anterior chamber. The cases in which the front membrane is only slightly broken are an intermediate form. In severe and complicated hernias, again (Fig. 6) miosis may be prevented by the vitreous filling the anterior chamber, especially if some of the more solid secondary vitreous has entered the chamber. Even with the strongest miotics it is then impossible to contract the pupil. This is also understandable, as by contracting, the iris prevents the vitreous from escaping from the anterior chamber, except possibly in cases where the vitreous is fluid.

Next—the actual prolapse and loss of the vitreous. In these cases the front membrane of the vitreous always ruptures. Under these circumstances it seems surprising that the loss of vitreous often remains comparatively small; sometimes it seems as if the slight flow would cease spontaneously. This may possibly be explained by the observations described above: the more liquid primary vitreous escapes first and then—if the intervening membrane ruptures—the secondary vitreous. An exception is the case in which the vitreous is more liquid and the difference in fluidity between the primary and secondary vitreous has disappeared. It is possible that the intervening membrane is then also weaker.

It is well known that whenever there is loss of vitreous, the risk of a persistent prolapse of the iris is great. The most severe case is an inversion of the iris (retroflexio iridis).

Now a few words as to the practical side of the question, the replacement of the prolapsed iris. I have already spoken of the important part of eserine in this reposition. For this purpose we have at our disposal the ordinary smooth iris spatula. Comberg has proposed a repositor with a ball end and a point on it. This, however, is so large that the wound must be opened too much and I, for my part, have not been able to use it satisfactorily. L. Müller already recommended the use of small forceps for the replacement of the iris prolapse and especially for retroversion of the iris. But this necessitates a rather wide opening of the wound. The most important requirement of a good repositor is that it can be used so that the cataract wound remains closed as much as possible.

The old smooth iris spatula satisfies this demand. But in severe cases it has the drawback that it cannot grip the iris but slips on its surface. Therefore we have made some of our spatulas with a small sharp needle-point. We place it into the eye perpendicularly and then it is easy to get hold of the iris.

An ordinary injection needle with a point suitably bent serves

the same purpose. The great advantage of this needle is that the wound need be opened minimally. A sharp cystitome can also be used. Both these instruments have the advantage that it is possible even in severe cases to grasp the posterior surface of the iris.

But how shall we manage the cases where the iris will repeatedly fall back into the wound after we already have succeeded in replacing it. Here, and generally in severe cases, I have observed that it helps to stretch and slightly press the iris. After getting a firm hold of the iris it should not be released but kept stretched towards the centre of the anterior chamber, then a slight and cautious pressure on the posterior surface of the cornea is applied, the nearer the periphery the better.

Considering the effect of such a centripetal stretching and postero-anterior pressure in the light of Figs. 5 and 6 it is apparent that it is an effective means of emptying the vitreous from the angle of the anterior chamber, which can be achieved by no miotics. And on the other hand, when this angle is emptied and the vitreous in the anterior chamber has diminished, the action of the eserine is stronger. Injury to the endothelium should, of course, be avoided.

Now the question arises whether there is a risk of rupturing the front membrane of the vitreous with the sharp point of the repositor? There is, but in all cases with real loss of vitreous, the front membrane is already ruptured; also, I have noticed that, where the cataract has been extracted intracapsularly after tumbling the lens, the front membrane was ruptured 8-10 days after the operation in about 8 per cent. of the cases, although the extraction was made without loss of vitreous.

When the delivery of the lens has been made directly without tumbling, this figure seems to be somewhat lower. It is thus possible that the membrane can be ruptured already with a simple careful reposition of the iris using the ordinary smooth spatula, or even as a result of extraction only. The replacement and avoiding of a prolapse is in any case more important than preserving the front membrane intact.

In cases where, in spite of our efforts, reposition does not succeed iridectomy is, of course, indicated. It should then extend as far as the root of the iris. After iridectomy a careful replacement of the iris is by no means less important than after extraction through a round pupil.

All that has been stated above concerns mainly the prolapse at extraction of the cataract. I do not intend to deal with the post-operative prolapse, but I should like to say that it is a complication the correction of which, I think, is more difficult than the cataract operation itself. Here it is most important that the patient is calm

and the eye as soft and insensible as possible (preferably cocaine). After that it is also important to insert the needle of the injection syringe perfectly painlessly into a conjunctival fold elevated by forceps. From this point work gradually to the deeper parts. An incautious handling of the needle can wholly spoil our work almost before we have started.

Summary

In animal tests and experiments on enucleated human eyes the writer has studied the front membrane of the vitreous. In many cases some vitreous comes out fairly easily and this prolapse seems to stop almost of its own accord, starting again only if the pressure on the bulb is further increased. A similar two-stage prolapse is rather often observed after the cataract operation, and it can be assumed that this is due to the fact that the primary vitreous (the space called post-lenticular by Koeppe and retro-lental by Vogt) extrudes first and that the more solid secondary vitreous prolapses only after the intervening membrane has ruptured.

On the basis of the writer's observations it depends essentially on the state of the front parts of the vitreous whether the size of the pupil can be reduced and the danger of prolapse of the iris and vitreous be avoided after cataract extraction. Especially after intracapsular extraction the vitreous tends to push into the anterior chamber as a fungus-like hernia. In simple hernias (front membrane of vitreous intact) the anterior chamber is usually of ordinary depth and the lower the hernia is, the more easily does the pupil contract with eserine. In complicated hernias of the vitreous (front membrane ruptured) the hernia is usually larger, the anterior chamber deeper, and the greater the quantity of vitreous that escapes into the anterior chamber, the less is the contracting effect of eserine on the pupil. In extreme cases the pupil which contracts after dropping in the eserine forms a " neck " which may even prevent the vitreous from escaping backwards from the anterior chamber. On this account we cannot in such cases reduce the size of the pupil even with the strongest miotics, at least not if some of the more solid secondary vitreous has also entered the anterior chamber.

In cases where replacement is difficult a good repositor of the iris should satisfy two requirements: first, such reposition should be possible that the cataract wound need only be slightly opened and, secondly, the instrument should have a sharp point in order to grasp the front surface of the iris; if necessary, it must be possible to grasp also the posterior surface when reposition with an ordinary smooth spatula cannot be done. An injection needle

with a bent point, a spatula equipped with a sharp point, and a small-size cystitome are recommended as repositors. In difficult cases one may try to express from between the iris and the cornea the vitreous that has extruded into the anterior chamber.

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ANNOTATIONS

Case Histories

The history of a case forms an essential part of any medical or surgical consultation. It depends largely on the type of patient you are dealing with whether the history is long drawn out or condensed. Some lady patients, of the type of Mrs. Nickleby, are exceedingly diffuse and far from clear headed. Not often does one meet such a laconic specimen as that recounted in Sir James Paget's Life. "What's that?" said a Yorkshireman, thrusting out his lower lip for inspection. "That's cancer" said Paget. "What's to be done with it?" "Cut it out." "What's your fee?" "Two guineas." We have all suffered in our time from the voluble lady who brings with her a reticule or attache case full of spectacles and prescriptions and means to have her money's worth in conversation if in nothing else.

As a general rule it is a wise plan to let the patient have her say without interruption. Occasionally it may be needful to ask a leading question, but these are best avoided if possible. A glaucoma case, that rushes in late for his appointment and says that his eye went funny a few days ago and that he wishes to be reassured as to its condition, should certainly be asked how his eye went funny; for he will probably present you with the diagnosis by saying

that he saw a coloured ring round a light. But the lady O.P. who wastes your time by informing you how her son was apprenticed to a carpenter and how her grandmother was stricken with creeping paralysis can be pulled up short, when it will be found as often as not that she has merely come to have her lotion repeated.

Nowadays no surgeon is ever likely to experience such candour in a lady patient as was displayed by that Duchess, supposed to have been a daughter of James II, who said to doctor, "whatever you may think is the matter with me, always have an eye to the p-x."

It is our firm conviction that it always pays to listen carefully to what the patient has to say.

Hall Marks of Practice

In Victorian days the high-water mark of a consultant's practice was the presence of a Bishop on one's books. Members of the Peerage, Baronets, Knights, Judges, and even the landed gentry were not to be despised, but a Bishop gave the practice a distinction not otherwise obtainable. Bishops were at that time in shorter supply, if we may use a modern cliché, than nowadays. We do not say that a bishop in need of presbyopic aid might not call at the chemist or optician first. Less exalted members of the cloth and their wives often did. A respected aunt of the writer's, who was the wife of a suburban vicar, always got her glasses at the chemists' and preferred so doing to being seen gratis by her nephew. The future seems to envisage a dead level of mediocrity. The state will pay whether the patient be a bishop or the humblest cottager in his diocese. That section of the community that does not matter a tinker's curse will be just as well off for ophthalmic treatment as the tinker.

FACULTY OF OPHTHALMOLOGISTS

The following rules of procedure to be proposed at the beginning of each Annual General Meeting have been agreed :—

1. Each item on the Agenda shall be read out by the President or an Officer.

2. Any Member or Associate wishing to speak on this item shall thereupon raise his hand, but shall not stand and speak until called upon by the President.

3. Each member shall speak for not more than five minutes when the President shall rise. The President may at his discretion ask a speaker to continue.

4. When the President considers that sufficient time and consideration have been given to an item on the Agenda he shall announce that the next business shall now be proceeded with, unless it is proposed and seconded and approved by the meeting that the discussion be continued.

5. Any member wishing to put a resolution or to raise a point of order shall stand although the President or another member may be standing, and shall remain standing until the President has taken note of his proposal or protest.

Certain members of the Council were appointed to meet representatives of the Ministry of Health to discuss points connected with the Supplementary Ophthalmic Service. In the meantime the Negotiating Committee resumed operations and the Ophthalmic Sub-Committee of the Negotiating Committee, of which the same Faculty representatives were members, met the Ministry on two occasions to consider the fees for the testing of sight under the Supplementary Service. As a result of these negotiations the Ministry agreed to the payment of £1 11s. 6d. per case on the condition that the work would be carried out on premises and with equipment provided by the ophthalmic medical practitioner. The question of G.P. ophthalmologists caused some difficulty and the fee was fixed on the understanding that not less than 95 per cent. of the work would be carried out by ophthalmologists of specialist status. The Ministry agreed that specialist status should include anyone who held an ophthalmic diploma, even though they might be engaged in general practice.

It has been stated that at the present time there is no possibility of a patient obtaining glasses through the Service if he visits an ophthalmologist privately. The Council has agreed that the question shall be raised with the Ministry again and the matter taken up with the Negotiating Committee.

The Ministry of Health has raised the question of the application of Supplementary Ophthalmic Service fees to ophthalmologists examining school children. The fee of £1 11s. 6d. was settled on the basis that a refraction took half-an-hour. School children are seen at a much faster rate and ophthalmologists carrying out this work are receiving more money than they should. Representatives of the Faculty are to discuss this matter with the Ministry of Health and the Ministry of Education, and it has been agreed to try and arrange for school clinic work to be carried out on a sessional basis, the remuneration to be based on the Spens Report.

The remuneration for medical officers carrying out refraction work in Hospital has been considered by the Council. Since the appointed day the remuneration received has been £4 per half-day, during which time six patients are seen, *i.e.*, at the rate of 13s. 4d.

per patient. Payment under the Supplementary Service is £1 11s. 6d. per case. The Council has reiterated its opinion that the Supplementary Service should not be carried out in Hospital and have agreed that remuneration for refraction work in Hospital should be on a sessional rate, based on the Spens Report. It has been decided to take the matter up with the Ministry of Health, together with various other points regarding the establishment of the Ophthalmic Sub-Committees of the Regional Boards, the position of the dispensing opticians in Hospitals and the employment of refracting opticians in Hospitals under the Final Service.

With regard to the circular issued by the B.M.A. requesting ophthalmic surgeons to place their names on a list in connection with the Supplementary Ophthalmic Service and stating that this did not entail taking part in the Service, it has been decided to point out to the Ministry of Health and to the B.M.A. that such a list cannot be regarded as representing those members of the specialty capable or desirous of taking part in the Final Service nor can it be regarded as comprehensive.

As regards remuneration for teaching, it has been agreed to refer the matter to the Negotiating Committee and the Royal College of Surgeons' Council and to press for the implementation of the Spens Report, which regards provisions for clinical work and teaching as entirely separate. It has been pointed out that in the Spens Committee the representative of the University Grants Committee was unwilling to discuss the remuneration for teaching.

The following resolution, passed at a meeting of a hundred ophthalmologists held during the Oxford Ophthalmological Congress, has been received by the Council:—

> "That the Ophthalmic Group Committee (or the Section of the Negotiating Committee dealing with ophthalmic matters) should be urged to provide fuller and more prompt information to Ophthalmologists who felt themselves to be inadequately served in this matter."

It has been agreed that, in the autumn, a memorandum should be circulated to all members of the Faculty, giving the present political position regarding ophthalmology.

The fee payable to ophthalmic surgeons for the examination of cases referred by Medical Boards has been raised. The present fee is 15s. per case. The Council is of the opinion that this service should come within the Supplementary Ophthalmic Service and that the fee should be £1 11s. 6d. per case.

With regard to the question of the lectures in ophthalmology at the Royal College of Surgeons, it has been agreed that it would be better to have seven or eight lectures at intervals during the year rather than to have a fortnightly course of lectures. This suggestion is to be considered by the Royal College of Surgeons.

SIR JOHN PARSONS' EIGHTIETH BIRTHDAY

Presentation of a Portrait

ON September 3, the occasion of his eightieth birthday, Sir John H. Parsons was presented with his portrait painted in oils by Mr. John Gilroy. The portrait was subscribed for by members of the Faculty of Ophthalmologists and the Ophthalmological Society of the United Kingdom and was presented to him by Sir Stewart Duke-Elder, President of the Faculty, at a widely attended ceremony in the library of the Royal College of Surgeons of England.

After confessing the immense debt which he personally owed Sir John Parsons, the President said that the portrait was presented to him for two reasons: as a token of admiration and gratitude for what he had done for ophthalmology and as an expression of the affection which his friends and pupils of two generations felt for him. He pointed out that for more than a generation Parsons had been the acknowledged leader in all aspects of British ophthalmology — in clinical work, fundamental research and public activities. For more than a generation he had been among the foremost consultants in the clinical practice of his specialty. So long as ophthalmology is a science he will be remembered as a pioneer in ophthalmic pathology for the work he did some fifty years ago. To-day he is still the foremost authority in the fundamental sciences concerning vision — biological, physiological and psychological. In guiding, stimulating and encouraging ophthalmic research in Great Britain he has in his time stood out almost alone; in all problems concerning vision successive governments and industry have consistently asked and received his help; he served in two world wars, in the first as Consultant to the Army, in the second as adviser to the Royal Air Force; in international ophthalmology he has long been a leading figure and has frequently been an acceptable and gracious British ambassador abroad; and for many years he was the dominant figure in the social and political life of the ophthalmologists in this country. Probably the greatest contribution, however, he made to ophthalmological life in England is the historical continuity he has succeeded in maintaining between the past and the future. In his youth British ophthalmology occupied a high place among the nations; but later, particularly in the inter-war years — largely because with the evolution of scientific techniques, individual effort had to give place to organized effort for which we were not prepared or equipped — English ophthalmology has tended to lose its place. He was largely responsible for stimulating it and if its future is as great or greater than its past, it will be largely due to his sustained and tireless efforts.

Sir John Parsons was further entertained at a dinner held in the

evening at the Royal College of Surgeons at which were present the members of the Councils of the Faculty, the Ophthalmological Society, the Ophthalmological Section of the Royal Society of Medicine and the Editorial Committee of the British Journal of Ophthalmology. Mr. F. Juler, the president of the Society, proposed the health of the octogenarian but extremely active guest. Mr. F. W. Law proposed the health of the artist and Sir Stewart Duke-Elder presented Sir John Parsons with a bound copy of the special September number of the Journal written in his honour.

BOOK NOTICES

A Handbook of Ophthalmolgy. By HUMPHREY NEAME and F. A. WILLIAMSON-NOBLE. Sixth edition. Pp. x and 336. Forty-nine coloured illustrations, 189 text figures. London: J. and A. Churchill. Price, 21/-. 1948.

In spite of the war no less than five editions of this book have appeared within the past thirteen years, a fact which may be taken as a well deserved tribute to its usefulness and popularity. The book is intended for undergraduate students and general practitioners, and confines itself largely to the more common diseases and practical methods of treatment. Changes in the new edition make it more up-to-date, information being given on the use of penicillin, the pathology of diabetic retinopathy, the causes of proptosis in thyroid dysfunction, and the pharmacological mode of action of miotics and mydriatics. The book within the spheres for which it is intended deserves, and we are sure will receive, a warm welcome.

Tabulae Biologicae. Vol. XXII (Oculus). Pars. 1. 408 pages. W. Junk, Amsterdam. 1947.

It will be remembered that the first volume of Tabulae Biologicae appeared in 1925: it was a German work published from Berlin, the contributors being derived with one exception from Germany and Austria. The twenty-second volume which has appeared recently is published from Amsterdam under the general editorship of Kurt Steindorff (late of Berlin), F. P. Fischer of Utrecht, J. S. Friedenwald of Baltimore and A. Sorsby of London. Steindorff was associated with the work from its inception. It will be remembered that in 1909 he published the first treatise on the chemistry of the eye which appeared in Oppenheimer's *Handbuch der Biochemie.* A refugee from Hitler, he spent the last years of his life in poverty in St. Juéry in the South of France compiling the present volume on ophthalmology. He died in 1942; but this production is essentially his inspiration and it is a pre-war compilation.

This volume, which is the first devoted entirely to the eye, contains seven sections—comparative anatomy of non-vertebrates by H. Kahmann of Munich, anatomical data and measurements of the eyes of man and animals by S. Oppenheim of Lautrach, embryology of the vertebrate eye by C. Dejean and F. Granel of Montpellier, descriptive anatomy of the eye by K. Steindorff, the pupil of vertebrates by J. Nordmann of Strasbourg, the intra-ocular pressure and the vascular pressures of the eye by K. W. Ascher.

The book follows the pattern of its predecessors and is a factual summary arranged in tabular form of the results of researches in the literature. It is, of course, a mine of information drawn from an enormous variety of sources with bibliographical references and is an immense time-saver for the research student. Its value, however, would be enhanced manifold if an index were appended.

CORRESPONDENCE

CLINICAL OPHTHALMOLOGY (for General Practitioners and Students)

To the Editors of THE BRITISH JOURNAL OF OPHTHALMOLOGY.

DEAR SIRS,—That my little book should have shocked your reviewer is gratifying, but as an old teacher for many years of ophthalmoscopy to under- and post-graduates I regret that the shock should have been so severe as to lead him to infer (surely a *non sequitur!*) that the medical students of Edinburgh are discouraged in the use of the ophthalmoscope. The scope and limitations of the book are set forth in the preface—why emphasise further that which is already adequately dealt with in existing works?

Sincerely yours,

H. M. TRAQUAIR.

16, MANOR PLACE,
EDINBURGH.
July 27, 1948.

NOTES

Appointments DR. S. N. Mitter has been appointed Professor of Ophthalmology, Medical College, Lucknow, U.P., India.

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Note THE Editors express regret that Professor W. Kapuscinski's paper published in the May number of this Journal contained a number of errors committed in translation from Polish to English. Professor Kapuscinski did not receive the galley proofs in time to correct these mistakes before the May number went to press. He has kindly agreed to write a short paper correcting these errors which we hope to publish in the near future.

* * * *

The Functions and Design of Hospitals THE Nuffield Provincial Hospitals Trust and the University of Bristol are jointly sponsoring an investigation into the functions and design of hospitals. Its aim will be a thorough study of hospital requirements in present-day society, from the human, the administrative and the environmental angles.

No better time than the present could be found to launch the investigation. The burden on many existing hospitals, which will be further increased by the provisions of the National Health Service Act, is aggravated by the obsolete buildings in which their work is done. It is unlikely that conditions will allow of any major building projects for a number of years and it is therefore vital that the years of waiting should be well spent in preparation. The *Hospital Surveys* (London: H.M. Stationery Office, 1945) showed an "overall inadequacy of accommodation" and in considering the essential problem of making the full range of first-class hospital treatment available to all who need it, many of the surveyors were deeply concerned "about the magnitude of the building programme . . . forced upon us by inexorable facts." This combination of circumstances favouring the investigation — the time-lag which must ensue before any large-scale building can be started coupled with the knowledge that such building must, almost inevitably be undertaken in the near future — is further reinforced by the currency of the belief that a full re-examination of the purpose and pattern of hospital provision is now overdue.

Not only will the investigators need to put themselves in the place of the patients and of the workers in hospital and look with fresh unprejudiced eyes at the planning of hospitals; they will also look

very carefully at the distribution of work in caring for the sick and in promoting health to see whether improvments might be brought about by an alteration in the balance of work now shared between hospitals, general practitioners and other health agencies.

If the project is to succeed it must offer practical guidance to those responsible for hospital design and internal organization in time for use to be made of it in the planning of new buildings. The research programme, rigorously objective and scientific in its methods though it will be, will yet concentrate on those aspects of the problem whose solution within the two or three-year period of the enquiry can reasonably be expected. If, as the sponsors hope, universities and other appropriate bodies collaborate by undertaking related research of longer range and of a more fundamental nature, our understanding of the proper functions and design of hospitals will be steadily supplemented and improved, even after the present enquiry is complete.

The investigation made, as it is, under the auspices of two independent organisations, will provide an outlet for interested private bodies to continue to do their share in improving hospital facilities by providing facts and advice helpful to those responsible for administering the National Health Service.

The conduct of the enquiry and the preparation of the report have been entrusted to a whole-time research team, to include members drawn from a variety of professions, medicine and nursing, social science and social welfare, architecture and engineering. Each member will contribute by a study of those problems of which he has special knowledge and will also share in shaping the programme as a whole. While seeking the proper development of the British tradition, steps will be taken to obtain and test the views and experience of those who have been concerned with the construction of hospitals in other countries. The investigation will run alongside the Hospital Job-Analysis already being undertaken for the Nuffield Provincial Hospitals Trust. It is expected that the findings of the job-analysis may throw considerable light upon some of the problems which will confront the new team.

Mr. L. Farrer-Brown, Secretary of the Nuffield Provincial Hospitals Trust, is acting as co-ordinating Chaiman of the enquiry. The Director of Research is Mr. John Madge, M.A., A.R.I.B.A., who has been seconded from his work at the University of Bristol for the purpose.

The research team will have the assistance of a panel of expert advisers composed of leading men and women in the fields affected by the investigation. It is hoped that the fact that their help and advice have been sought will give assurance that all authoritative points of view are to be considered and that the full weight of practical experience will be brought to bear on the enquiry.

Use of Rubber Gloves

DR. F. W. SIMPSON, M.B., B.S. (Adelaide), has written us a letter in which he comments that it is exceptional to see surgeons, assistants and the theatre sisters in the Eye Hospitals of London wearing rubber gloves. He reminds us of the high standards of aseptic technique practised by the orthopaedic surgeons and ends his letter by asking — "What is there in eye surgery that renders it immune from the laws of asepsis?"

As I am one of the exceptions who wear gloves for most eye operations I agree with Dr. Simpson's justifiable comments. It is, I am sure, very desirable for assistants and sisters handling instruments to wear gloves for intra-ocular operations even when the surgeon does not do so himself but relies on as perfect a non-touch technique as it is possible to practice. Serious intra-ocular infection has followed squint and retinal detachment operations in a few cases where gloves have not been worn and sutures have been handled carelessly. Although such catastrophes happen rarely they are reminders of serious imperfections in technique. It is both fortunate and unfortunate that the ungloved so often get away with the risks they run.

There is, however, no doubt that gloves hamper delicate intra-ocular manoeuvres and in such cases there is this justification for their omission, particular care being taken that the surgeon's hands are thoroughly washed, rinsed in desogen, dried thoroughly in a sterile towel (after a clean gown has been put on so that the towel does not contact unwashed forearms) the instruments are dry and not wet, that nothing touches the skin or conjunctiva before entering the eye and that the assistants wear gloves.

It is taking unjustifiable risks to do plastic operations, operations involving bone, squints and retinal detachments without gloves.

We are grateful to Dr. Simpson for his correct and candid comments.

H.B.S. (Assistant Editor).

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Sociedade de Oftalmologia de Minas Gerais (Brasil) Officers, 1948

THE following officers have been elected for the current Sessions. *President:* Dr. C. Laborne Tavares, *Vice-President:* Dr. Odilon Alves, *Secretary:* Dr. Creso Barbi, *Treasurer:* Dr. Angelo Laborne Tavares, *Librarian:* Dr. Antonio Isidoro.

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Ophthalmology in Roumania

TWO new Ophthalmological Societies have been recently founded in Roumania. (*a*) Société Roumaine d'oculistique: President, Dr. Nicholas Blatt. General Secretary, Dr. Nicholas Zolog, on

December 3, 1947. (*b*) Société Roumaine de Prophylaxie de la Cécité: President, Dr. Nicholas Blatt. General Secretary, Dr. Virgil Popovici, on December 30, 1947. We wish both Societies all success in the future.

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University of Glasgow Department of Ophthalmology Autumn, 1948

DURING the month of October a series of meetings will be held in the Department on Wednesdays at 8 p.m. The General Arrangements will be similar to the series held last year. Tea will be served after the paper and a discussion will follow. The meetings will be open to all medical practitioners and senior students interested in Ophthalmology.

October 6—Mr. Frank W. Law, "Physiotherapy of the Eye."
October 13—Dr. Paul Hacsich, "Experimental Corneal Grafting."
October 20—Dr. Byron Smith, "Plastic Surgery of the Eyelids."
October 27—Prof. Loewenstein, "Histopathology of the Drainage Angle."

* * * *

Ophthalmic Prescriptions

THE method of writing an ophthalmic prescription generally accepted in this country and in the United States is:—

Right Eye: Sphere..... Cylinder.....
Left Eye: Sphere..... Cylinder.....

A large firm of optical manufacturers points out that some doctors now practising in this country write prescriptions in the reverse way — the cylinder written first instead of the sphere, and the left eye first instead of the right. In many cases these prescriptions are passed on to manufacturers whose staffs are trained in the conventional way of reading them with the result that a large number of returns are incurred which could be avoided if all doctors adhered to the normal practice.

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Corrigendum

IN the matter of back numbers of the Journal, referred to in a note on page 516, we would call attention to an error. January 1942 should have read January 1924.